HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PADCEV safely and effectively. See full prescribing information for PADCEV.

PADCEV® (enfortumab vedotin-ejfv) for injection, for intravenous use
Initial U.S. Approval: 2019

WARNING: SERIOUS SKIN REACTIONS

See full prescribing information for complete boxed warning.

- **PADCEV can cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).**
- **Immediately withhold PADCEV and consider referral for specialized care for suspected SJS or TEN or severe skin reactions.**
- **Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions. (2.2), (5.1), (6.1)**

RECENT MAJOR CHANGES

Indications and Usage (1)	11/2025
Dosage and Administration (2.1)	11/2025
Warnings and Precautions (5.1), (5.3), (5.4)	11/2025

INDICATIONS AND USAGE

PADCEV is a Nectin-4-directed antibody and microtubule inhibitor conjugate indicated:

- in combination with pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph, as neoadjuvant treatment and then continued after cystectomy as adjuvant treatment, for the treatment of adult patients with muscle invasive bladder cancer (MIBC) who are ineligible for cisplatin-containing chemotherapy. (1)
- in combination with pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph, for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC). (1)
- as a single agent for the treatment of adult patients with locally advanced or mUC who:
  - have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and platinum-containing chemotherapy, or
  - are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy. (1)

DOSAGE AND ADMINISTRATION

- *For intravenous infusion only.* Do not administer PADCEV as an intravenous push or bolus. Do not mix with, or administer as an infusion with, other medicinal products. (2.3)
- MIBC: The recommended dose of PADCEV in combination with pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph is 1.25 mg/kg (up to a maximum dose of 125 mg) given as an intravenous infusion over 30 minutes. PADCEV is administered as neoadjuvant treatment on Days 1 and 8 of each 21-day cycle for 3 cycles or until disease progression that precludes curative intent cystectomy or unacceptable toxicity, followed by adjuvant treatment on Days 1 and 8 of each 21-day cycle for 6 cycles or until disease recurrence or unacceptable toxicity. (2.1)
- Locally Advanced or mUC: The recommended dose of PADCEV in combination with pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph is 1.25 mg/kg (up to a maximum dose of 125 mg) given as an intravenous infusion over 30 minutes on Days 1 and 8 of a 21-day cycle until disease progression or unacceptable toxicity. (2.1)
- The recommended dose of PADCEV as a single agent is 1.25 mg/kg (up to a maximum dose of 125 mg) given as an intravenous infusion over 30 minutes on Days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity. (2.1)
- Avoid use in patients with moderate or severe hepatic impairment. (8.6)

DOSAGE FORMS AND STRENGTHS

For Injection: 20 mg and 30 mg of enfortumab vedotin-ejfv as a lyophilized powder in a single-dose vial for reconstitution. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Hyperglycemia: Diabetic ketoacidosis may occur in patients with and without preexisting diabetes mellitus, which may be fatal. Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia. Withhold PADCEV if blood glucose is >250 mg/dL. (2.2, 5.2)
- Pneumonitis/Interstitial Lung Disease (ILD): Severe, life-threatening or fatal pneumonitis/ILD may occur. Withhold PADCEV for Grade 2 pneumonitis/ILD and consider dose reduction. Permanently discontinue PADCEV for Grade 3 or 4 pneumonitis/ILD. (2.2, 5.3)
- Peripheral Neuropathy: Monitor patients for new or worsening peripheral neuropathy and consider dose interruption, dose reduction, or discontinuation of PADCEV. (2.2, 5.4)
- Ocular Disorders: Ocular disorders, including vision changes, may occur. Monitor patients for signs or symptoms of ocular disorders. Consider prophylactic artificial tears for dry eyes and treatment with ophthalmic topical steroids after an ophthalmic exam. Consider dose interruption or dose reduction of PADCEV when symptomatic ocular disorders occur. (5.5)
- Infusion Site Extravasation: Ensure adequate venous access prior to administration. Monitor the infusion site during PADCEV administration and stop the infusion immediately for suspected extravasation. (5.6)
- Embryo-Fetal Toxicity: PADCEV can cause fetal harm. Advise of the potential risk to a fetus and to use effective contraception. (5.7, 8.1, 8.3)

ADVERSE REACTIONS

The most common adverse reactions, including laboratory abnormalities, (≥20%) were:

- PADCEV in combination with intravenous pembrolizumab for the treatment of MIBC: increased glucose, decreased hemoglobin, increased aspartate aminotransferase, rash, increased alanine aminotransferase, fatigue, pruritus, increased creatinine, decreased sodium, decreased lymphocytes, peripheral neuropathy, increased potassium, alopecia, dysgeusia, diarrhea, decreased appetite, constipation, nausea, decreased phosphate, urinary tract infection, dry eye, and decreased weight. (6.1)
- PADCEV in combination with intravenous pembrolizumab for the treatment of locally advanced or mUC: increased aspartate aminotransferase, increased creatinine, rash, increased glucose, peripheral neuropathy, increased lipase, decreased lymphocytes, increased alanine aminotransferase, decreased hemoglobin, fatigue, decreased sodium, decreased phosphate, decreased albumin, pruritus, diarrhea, alopecia, decreased weight, decreased appetite, increased urate, decreased neutrophils, decreased potassium, dry eye, nausea, constipation, increased potassium, dysgeusia, urinary tract infection, and decreased platelets. (6.1)
- PADCEV as a single agent: increased glucose, increased aspartate aminotransferase, decreased lymphocytes, increased creatinine, rash, fatigue, peripheral neuropathy, decreased albumin, decreased hemoglobin, alopecia, decreased appetite, decreased neutrophils, decreased sodium, increased alanine aminotransferase, decreased phosphate, diarrhea, nausea, pruritus, increased urate, dry eye, dysgeusia, constipation, increased lipase, decreased weight, decreased platelets, abdominal pain, and dry skin. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Astellas Pharma US, Inc. at 1-800-727-7003 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

Concomitant use of dual P-gp and strong CYP3A4 inhibitors with PADCEV may increase the exposure to monomethyl auristatin E (MMAE). (7.1)

USE IN SPECIFIC POPULATIONS

- Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 11/2025

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: SERIOUS SKIN REACTIONS

- **PADCEV can cause severe and fatal cutaneous adverse reactions including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), which occurred predominantly during the first cycle of treatment, but may occur later.**
- **Closely monitor patients for skin reactions.**
- **Immediately withhold PADCEV and consider referral for specialized care for suspected SJS or TEN or severe skin reactions.**
- **Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions *[see Dosage and Administration (2.2), Warnings and Precautions (5.1), and Adverse Reactions (6.1)].***

1 INDICATIONS AND USAGE

PADCEV®, in combination with pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph, as neoadjuvant treatment and then continued after cystectomy as adjuvant treatment, is indicated for the treatment of adult patients with muscle invasive bladder cancer (MIBC) who are ineligible for cisplatin-containing chemotherapy.

PADCEV®, in combination with pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph, is indicated for the treatment of adult patients with locally advanced or metastatic urothelial cancer (mUC).

PADCEV, as a single agent, is indicated for the treatment of adult patients with locally advanced or mUC who:

- have previously received a programmed death receptor-1 (PD-1) or programmed death-ligand 1 (PD-L1) inhibitor and platinum-containing chemotherapy, or
- are ineligible for cisplatin-containing chemotherapy and have previously received one or more prior lines of therapy.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosage

The recommended dosages for PADCEV in combination with pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph, and PADCEV as a single agent are presented in Table 1 and Table 2.

Administer PADCEV as an intravenous infusion over 30 minutes as recommended [see *Instructions for Preparation and Administration (2.3)*]. Administer PADCEV prior to pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph if administering on the same day.

Table 1. Recommended Dosages for PADCEV in combination with pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph[1]

Indication	Recommended PADCEV Dosage	Duration of Therapy
Neoadjuvant and Adjuvant Muscle Invasive Bladder Cancer (MIBC)	PADCEV 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) on Days 1 and 8 of a 21-day cycle.	Neoadjuvant: 3 cycles or until disease progression that precludes curative intent cystectomy or unacceptable toxicity. Adjuvant: 6 cycles or until disease recurrence or unacceptable toxicity.
Locally advanced or metastatic Urothelial Cancer (mUC)	PADCEV 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) on Days 1 and 8 of a 21-day cycle.	Until disease progression or unacceptable toxicity.

1. Administer PADCEV prior to pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph if administering on the same day. For the recommended dosage of pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph, refer to the respective Prescribing Information.

Table 2. Recommended Dosages for PADCEV as a single agent

Indication	Recommended PADCEV Dosage	Duration of Therapy
Locally advanced or metastatic Urothelial Cancer (mUC)	PADCEV 1.25 mg/kg (up to a maximum of 125 mg for patients ≥100 kg) on Days 1, 8, and 15 of a 28-day cycle.	Until disease progression or unacceptable toxicity.

2.2 Dose Modifications

Table 3. Dose Modifications

Adverse Reaction	Severity[1]	Dose Modification[1]
Skin Reactions *[see Boxed Warning, Warnings and Precautions (5.1)]*	For persistent or recurrent Grade 2 skin reactions	Consider withholding until Grade ≤1, then resume treatment at the same dose level or dose reduce by one dose level.
	Grade 3 skin reactions	Withhold until Grade ≤1, then resume treatment at the same dose level or dose reduce by one dose level.
	Suspected SJS or TEN	Immediately withhold, consult a specialist to confirm the diagnosis. If not SJS/TEN, see Grade 2-4 skin reactions.
	Confirmed SJS or TEN; Grade 4 or recurrent Grade 3 skin reactions	Permanently discontinue.
Hyperglycemia *[see Warnings and Precautions (5.2)]*	Blood glucose >250 mg/dL	Withhold until elevated blood glucose has improved to ≤250 mg/dL, then resume treatment at the same dose level.
Pneumonitis/Interstitial Lung Disease (ILD) *[see Warnings and Precautions (5.3)]*	Grade 2	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade ≥3	Permanently discontinue.
Peripheral Neuropathy *[see Warnings and Precautions (5.4)]*	Grade 2	Withhold until Grade ≤1, then resume treatment at the same dose level (if first occurrence). For a recurrence, withhold until Grade ≤1, then resume treatment reduced by one dose level.
	Grade ≥3	Permanently discontinue.
Other Nonhematologic Toxicity *[see Adverse Reactions (6)]*	Grade 3	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4	Permanently discontinue.
Hematologic Toxicity *[see Adverse Reactions (6)]*	Grade 3, or Grade 2 thrombocytopenia	Withhold until Grade ≤1, then resume treatment at the same dose level or consider dose reduction by one dose level.
	Grade 4	Withhold until Grade ≤1, then reduce dose by one dose level or discontinue treatment.

1. Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

Table 4. Recommended Dose Reduction Schedule

Dose Reduction Schedule	Dose Level
Starting dose	1.25 mg/kg up to 125 mg
First dose reduction	1 mg/kg up to 100 mg
Second dose reduction	0.75 mg/kg up to 75 mg
Third dose reduction	0.5 mg/kg up to 50 mg

2.3 Instructions for Preparation and Administration

- Administer PADCEV as an intravenous infusion only.
- PADCEV is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

Prior to administration, the PADCEV vial is reconstituted with Sterile Water for Injection (SWFI). The reconstituted solution is subsequently diluted in an intravenous infusion bag containing either 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP.

Reconstitution in Single-Dose Vial

1. Follow procedures for proper handling and disposal of anticancer drugs.
2. Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.
3. Calculate the recommended dose based on the patient's weight to determine the number and strength (20 mg or 30 mg) of vials needed.
4. Reconstitute each vial as follows and, if possible, direct the stream of SWFI along the walls of the vial and not directly onto the lyophilized powder:
    a. 20 mg vial: Add 2.3 mL of SWFI, resulting in 10 mg/mL PADCEV.
    b. 30 mg vial: Add 3.3 mL of SWFI, resulting in 10 mg/mL PADCEV.
5. Slowly swirl each vial until the contents are completely dissolved. Allow the reconstituted vial(s) to settle for at least 1 minute until the bubbles are gone. DO NOT SHAKE THE VIAL. Do not expose to direct sunlight.
6. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted solution should be clear to slightly opalescent, colorless to light yellow, and free of visible particles. Discard any vial with visible particles or discoloration.
7. Based upon the calculated dose amount, the reconstituted solution from the vial(s) should be added to the infusion bag immediately. This product does not contain a preservative. If not used immediately, reconstituted vials may be stored for up to 24 hours in refrigeration at 2°C to 8°C (36°F to 46°F). DO NOT FREEZE. Discard unused vials with reconstituted solution beyond the recommended storage time.

Dilution in Infusion Bag

1. Withdraw the calculated dose amount of reconstituted solution from the vial(s) and transfer into an infusion bag.
2. Dilute PADCEV with either 5% Dextrose Injection, 0.9% Sodium Chloride Injection, or Lactated Ringer's Injection. The infusion bag size should allow enough diluent to achieve a final concentration of 0.3 mg/mL to 4 mg/mL PADCEV.
3. Mix diluted solution by gentle inversion. DO NOT SHAKE THE BAG. Do not expose to direct sunlight.
4. Visually inspect the infusion bag for any particulate matter or discoloration prior to use. The reconstituted solution should be clear to slightly opalescent, colorless to light yellow, and free of visible particles. DO NOT USE the infusion bag if particulate matter or discoloration is observed.
5. Discard any unused portion left in the single-dose vials.

Administration

1. Immediately administer the infusion over 30 minutes through an intravenous line.
2. If the infusion is not administered immediately, the prepared infusion bag should not be stored longer than 8 hours at 2°C to 8°C (36°F to 46°F). DO NOT FREEZE.

DO NOT administer PADCEV as an intravenous push or bolus.

DO NOT mix PADCEV with, or administer as an infusion with, other medicinal products.

3 DOSAGE FORMS AND STRENGTHS

For Injection: 20 mg and 30 mg of enfortumab vedotin-ejfv as a white to off-white lyophilized powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Skin Reactions

Severe cutaneous adverse reactions, including fatal cases of SJS or TEN occurred in patients treated with PADCEV. SJS and TEN occurred predominantly during the first cycle of treatment but may occur later.

Skin reactions occurred in 61% (all grades) of the 167 patients treated with PADCEV in combination with intravenous pembrolizumab for the treatment of MIBC in clinical trials. The majority of the skin reactions that occurred with combination therapy included rash and maculo-papular rash. Grade 3-4 skin reactions occurred in 10% of patients (Grade 3: 9%, Grade 4: 1.2%), including rash, maculo-papular rash, toxic skin eruption, dermatitis exfoliative generalized, erythema, exfoliative rash, skin toxicity, toxic epidermal necrolysis, and toxic erythema of chemotherapy. A fatal reaction of toxic epidermal necrolysis occurred in one patient (0.6%). The median time to onset of severe skin reactions was 0.6 months (range: 0.2 to 8.8 months). Skin reactions led to discontinuation of PADCEV in 10% of patients *[see Adverse Reactions (6.1)]*. Of the patients who experienced a skin reaction and had data regarding resolution (n=102), 83% had complete resolution and 17% had residual skin reactions at their last evaluation. Of the patients with residual skin reactions at last evaluation, 29% (5/17) had Grade ≥2 skin reactions.

Skin reactions occurred in 70% (all grades) of the 564 patients treated with PADCEV in combination with intravenous pembrolizumab for the treatment of locally advanced or mUC in clinical trials. When PADCEV was given in combination with intravenous pembrolizumab, the incidence of skin reactions, including severe events, occurred at a higher rate compared to PADCEV as a single agent. The majority of the skin reactions that occurred with combination therapy included maculo-papular rash, macular rash, and papular rash. Grade 3-4 skin reactions occurred in 17% of patients (Grade 3: 16%, Grade 4: 1%), including maculo-papular rash, bullous dermatitis, dermatitis, exfoliative dermatitis, pemphigoid, rash, erythematous rash, macular rash, and papular rash. A fatal reaction of bullous dermatitis occurred in one patient (0.2%). The median time to onset of severe skin reactions was 1.7 months (range: 0.1 to 17.2 months). Skin reactions led to discontinuation of PADCEV in 6% of patients *[see Adverse Reactions (6.1)]*. Of the patients who experienced a skin reaction and had data regarding resolution (n=391), 59% had complete resolution and 41% had residual skin reactions at their last evaluation. Of the patients with residual skin reactions at last evaluation, 27% (43/159) had Grade ≥2 skin reactions.

Skin reactions occurred in 58% (all grades) of the 720 patients treated with PADCEV as a single agent in clinical trials. Twenty-three percent (23%) of patients had maculo-papular rash and 34% had pruritus. Grade 3-4 skin reactions occurred in 14% of patients, including maculo-papular rash, erythematous rash, rash or drug eruption, symmetrical drug-related intertriginous and flexural exanthema (SDRIFE), bullous dermatitis, exfoliative dermatitis, and palmar-plantar erythrodysesthesia. The median time to onset of severe skin reactions was 0.6 months (range: 0.1 to 8 months). Among patients experiencing a skin reaction leading to dose interruption who then restarted PADCEV (n=75), 24% of patients restarting at the same dose and 24% of patients restarting at a reduced dose experienced recurrent severe skin reactions.

Skin reactions led to discontinuation of PADCEV in 3.1% of patients *[see Adverse Reactions (6.1)]*. Of the patients who experienced a skin reaction and had data regarding resolution (n=328), 58% had complete resolution and 42% had residual skin reactions at their last evaluation. Of the patients with residual skin reactions at last evaluation, 39% (53/137) had Grade ≥2 skin reactions.

Monitor patients closely throughout treatment for skin reactions. Consider topical corticosteroids and antihistamines, as clinically indicated.

For persistent or recurrent Grade 2 skin reactions, consider withholding PADCEV until Grade ≤1. Withhold PADCEV and refer for specialized care for suspected SJS, TEN or for Grade 3 skin reactions.

Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions *[see Dosage and Administration (2.2)]*.

5.2 Hyperglycemia

Hyperglycemia and diabetic ketoacidosis (DKA), including fatal events, occurred in patients with and without pre-existing diabetes mellitus, treated with PADCEV.

Patients with baseline hemoglobin A1C ≥8% were excluded from clinical trials.

In clinical trials of PADCEV as a single agent, 17% of the 720 patients treated with PADCEV developed hyperglycemia of any grade; 7% of patients developed Grade 3-4 hyperglycemia (Grade 3: 6.5%, Grade 4: 0.6%). Fatal events of hyperglycemia and diabetic ketoacidosis occurred in one patient each (0.1%). The incidence of Grade 3-4 hyperglycemia increased consistently in patients with higher body mass index and in patients with higher baseline A1C. The median time to onset of hyperglycemia was 0.5 months (range: 0 to 20 months). Hyperglycemia led to discontinuation of PADCEV in 0.7% of patients *[see Adverse Reactions (6.1)]*. Five percent (5%) of patients required initiation of insulin therapy for treatment of hyperglycemia. Of the patients who initiated insulin therapy for treatment of hyperglycemia, 66% (23/35) discontinued insulin by the time of last evaluation.

Closely monitor blood glucose levels in patients with, or at risk for, diabetes mellitus or hyperglycemia.

If blood glucose is elevated (>250 mg/dL), withhold PADCEV *[see Dosage and Administration (2.2)]*.

5.3 Pneumonitis/Interstitial Lung Disease (ILD)

Severe, life-threatening or fatal pneumonitis/ILD occurred in patients treated with PADCEV.

When PADCEV was given in combination with intravenous pembrolizumab for the treatment of MIBC, 4.2% of the 167 patients treated with combination therapy had pneumonitis/ILD of any grade. All events were Grade 1-2. The median time to onset of any grade pneumonitis/ILD was 2.5 months (range: 1.9 to 9.7 months).

When PADCEV was given in combination with intravenous pembrolizumab for the treatment of locally advanced or mUC, 10% of the 564 patients treated with combination therapy had pneumonitis/ILD of any grade and 4% had Grade 3-4. A fatal event of pneumonitis/ILD occurred in two patients (0.4%). The incidence of pneumonitis/ILD, including severe events, occurred at a higher rate when PADCEV was given in combination with intravenous pembrolizumab compared to PADCEV as a single agent. The median time to onset of any grade pneumonitis/ILD was 4 months (range: 0.3 to 26 months).

In clinical trials of PADCEV as a single agent, 3% of the 720 patients treated with PADCEV had pneumonitis/ILD of any grade and 0.8% had Grade 3-4. The median time to onset of any grade pneumonitis/ILD was 2.9 months (range: 0.6 to 6 months).

Monitor patients for signs and symptoms indicative of pneumonitis/ILD such as hypoxia, cough, dyspnea or interstitial infiltrates on radiologic exams. Evaluate and exclude infectious, neoplastic and other causes for such signs and symptoms through appropriate investigations.

Withhold PADCEV for patients who develop Grade 2 pneumonitis/ILD and consider dose reduction. Permanently discontinue PADCEV in all patients with Grade 3 or 4 pneumonitis/ILD *[see Dosage and Administration (2.2)]*.

5.4 Peripheral Neuropathy

When PADCEV was given in combination with intravenous pembrolizumab for the treatment of MIBC, 39% of the 167 patients treated with combination therapy had peripheral neuropathy of any grade, 12% had Grade 2 neuropathy, and 3% had Grade 3 neuropathy. The median time to onset of Grade ≥2 peripheral neuropathy was 4.7 months (range: 0.2 to 11 months) *[see Adverse Reactions (6.1)]*. Of the patients who experienced neuropathy and had data regarding resolution (n=65), 32% had complete resolution, and 68% of patients had residual neuropathy at last evaluation. Of the patients with residual neuropathy at last evaluation, 27% (12/44) had Grade ≥2 neuropathy.

When PADCEV was given in combination with intravenous pembrolizumab for the treatment of locally advanced or mUC, 67% of the 564 patients treated with combination therapy had peripheral neuropathy of any grade, 36% had Grade 2 neuropathy, and 7% had Grade 3 neuropathy. The incidence of peripheral neuropathy occurred at a higher rate when PADCEV was given in combination with intravenous pembrolizumab compared to PADCEV as a single agent. The median time to onset of Grade ≥2 peripheral neuropathy was 6 months (range: 0.3 to 25 months) *[see Adverse Reactions (6.1)]*. Of the patients who experienced neuropathy and had data regarding resolution (n=373), 13% had complete resolution, and 87% of patients had residual neuropathy at last evaluation. Of the patients with residual neuropathy at last evaluation, 45% (146/326) had Grade ≥2 neuropathy.

Peripheral neuropathy occurred in 53% of the 720 patients treated with PADCEV as a single agent in clinical trials including 38% with sensory neuropathy, 8% with muscular weakness, and 7% with motor neuropathy. Thirty percent of patients experienced Grade 2 reactions and 5% experienced Grade 3-4 reactions. Peripheral neuropathy occurred in patients treated with PADCEV with or without preexisting peripheral neuropathy. The median time to onset of Grade ≥2 peripheral neuropathy was 4.9 months (range: 0.1 to 20 months). Neuropathy led to treatment discontinuation in 6% of patients *[see Adverse Reactions (6.1)]*. Of the patients who experienced neuropathy who had data regarding resolution (n=296), 11% had complete resolution, and 89% had residual neuropathy at the time of their last evaluation. Of the patients with residual neuropathy at last evaluation, 50% (132/262) had Grade ≥2 neuropathy.

Monitor patients for symptoms of new or worsening peripheral neuropathy and consider dose interruption or dose reduction of PADCEV when peripheral neuropathy occurs.

Permanently discontinue PADCEV in patients who develop Grade ≥3 peripheral neuropathy *[see Dosage and Administration (2.2)]*.

5.5 Ocular Disorders

Ocular disorders were reported in 40% of the 384 patients treated with PADCEV as a single agent in clinical trials in which ophthalmologic exams were scheduled. The majority of these events involved the cornea and included events associated with dry eye such as keratitis, blurred vision, increased lacrimation, conjunctivitis, limbal stem cell deficiency, and keratopathy.

Dry eye symptoms occurred in 30% of patients, and blurred vision occurred in 10% of patients, during treatment with PADCEV. The median time to onset to symptomatic ocular disorder was 1.7 months (range: 0 to 30.6 months). Monitor patients for ocular disorders. Consider artificial tears for prophylaxis of dry eyes and ophthalmologic evaluation if ocular symptoms occur or do not resolve. Consider treatment with ophthalmic topical steroids, if indicated after an ophthalmic exam. Consider dose interruption or dose reduction of PADCEV for symptomatic ocular disorders.

5.6 Infusion Site Extravasation

Skin and soft tissue reactions secondary to extravasation have been observed after administration of PADCEV. Of the 720 patients treated with PADCEV as a single agent in clinical trials, 1% of patients experienced skin and soft tissue reactions, including 0.3% who experienced Grade 3-4 reactions. Reactions may be delayed. Erythema, swelling, increased temperature, and pain worsened until 2-7 days after extravasation and resolved within 1-4 weeks of peak. Two patients (0.3%) developed extravasation reactions with secondary cellulitis, bullae, or exfoliation. Ensure adequate venous access prior to starting PADCEV and monitor for possible extravasation during administration. If extravasation occurs, stop the infusion and monitor for adverse reactions.

5.7 Embryo-Fetal Toxicity

Based on the mechanism of action and findings in animals, PADCEV can cause fetal harm when administered to a pregnant woman. In animal reproduction studies, administration of enfortumab vedotin-ejfv to pregnant rats during the period of organogenesis caused maternal toxicity, embryo-fetal lethality, structural malformations and skeletal anomalies at maternal exposures similar to the clinical exposures at the recommended human dose of 1.25 mg/kg.

Advise patients of the potential risk to the fetus. Advise female patients of reproductive potential to use effective contraception during treatment with PADCEV and for 2 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose *[see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.1)]*.

6 ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the labeling:

- Skin Reactions *[see Boxed Warning, Warnings and Precautions (5.1)]*
- Hyperglycemia *[see Warnings and Precautions (5.2)]*
- Pneumonitis/Interstitial Lung Disease (ILD) *[see Warnings and Precautions (5.3)]*
- Peripheral Neuropathy *[see Warnings and Precautions (5.4)]*
- Ocular Disorders *[see Warnings and Precautions (5.5)]*
- Infusion Site Extravasation *[see Warnings and Precautions (5.6)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety population described in the WARNINGS AND PRECAUTIONS reflect exposure to PADCEV 1.25 mg/kg in combination with intravenous pembrolizumab for the treatment of MIBC in 167 patients in EV-303 (NCT03924895) and for the treatment of locally advanced or mUC in 564 patients in EV-302 (NCT04223856) and EV-103 (NCT03288545); PADCEV as a single agent at 1.25 mg/kg in 720 patients in EV-301 (NCT03474107), EV-201 (NCT03219333), EV-203 (NCT04995419), EV-101 (NCT02091999), and EV-102 (NCT03070990). Ocular disorders reflect 384 patients in EV-201, EV-101, and EV-102.

Among 167 patients receiving PADCEV in combination with intravenous pembrolizumab for the treatment of MIBC, the most common (≥20%) adverse reactions, including laboratory abnormalities, were increased glucose, decreased hemoglobin, increased aspartate aminotransferase, rash, increased alanine aminotransferase, fatigue, pruritus, increased creatinine, decreased sodium, decreased lymphocytes, peripheral neuropathy, increased potassium, alopecia, dysgeusia, diarrhea, decreased appetite, constipation, nausea, decreased phosphate, urinary tract infection, dry eye, and decreased weight.

Among 564 patients receiving PADCEV in combination with intravenous pembrolizumab for the treatment of locally advanced or mUC, 59% were exposed to PADCEV for ≥6 months, and 24% were exposed for ≥12 months. In this pooled population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were increased aspartate aminotransferase, increased creatinine, rash, increased glucose, peripheral neuropathy, increased lipase, decreased lymphocytes, increased alanine aminotransferase, decreased hemoglobin, fatigue, decreased sodium, decreased phosphate, decreased albumin, pruritus, diarrhea, alopecia, decreased weight, decreased appetite, increased urate, decreased neutrophils, decreased potassium, dry eye, nausea, constipation, increased potassium, dysgeusia, urinary tract infection, and decreased platelets.

Among 720 patients receiving PADCEV as a single agent, 37% were exposed for ≥6 months, and 14% were exposed for ≥12 months. In this pooled population, the most common (≥20%) adverse reactions, including laboratory abnormalities, were increased glucose, increased aspartate aminotransferase, decreased lymphocytes, increased creatinine, rash, fatigue, peripheral neuropathy, decreased albumin, decreased hemoglobin, alopecia, decreased appetite, decreased neutrophils, decreased sodium, increased alanine aminotransferase, decreased phosphate, diarrhea, nausea, pruritus, increased urate, dry eye, dysgeusia, constipation, increased lipase, decreased weight, decreased platelets, abdominal pain, and dry skin.

The data described in the following section reflects exposure to PADCEV in combination with intravenous pembrolizumab from EV-302, the dose escalation cohort, Cohort A and Cohort K of EV-103, and EV-303. Patients received PADCEV 1.25 mg/kg in combination with intravenous pembrolizumab until disease progression or unacceptable toxicity.

The data described in the following section also reflects exposure to PADCEV as a single agent from an open-label, randomized, trial (EV-301) and Cohort 1 and Cohort 2 of an open-label, single arm, two cohort trial (EV-201). Patients received PADCEV 1.25 mg/kg until disease progression or unacceptable toxicity.

Neoadjuvant and Adjuvant Treatment of Cisplatin-Ineligible Patients with MIBC

EV-303

The safety of PADCEV in combination with intravenous pembrolizumab as neoadjuvant treatment and continued after radical cystectomy (RC) as adjuvant treatment was evaluated in an open-label, randomized, multicenter trial (EV-303) in patients with previously untreated MIBC who were ineligible for or declined cisplatin-based chemotherapy. Patients received PADCEV 1.25 mg/kg in combination with intravenous pembrolizumab (n=167) before and after RC with pelvic lymph node dissection (PLND) or RC with PLND alone (n=159) *[see Clinical Studies (14)]*.

For the 167 patients who received PADCEV in the neoadjuvant phase, the median duration of exposure to PADCEV was 1.6 months (range: 0.03 to 2.8 months) and the median number of cycles of PADCEV was 3 (range: 1, 3) in the neoadjuvant phase. For the 92 patients who received PADCEV in the adjuvant phase, the median duration of exposure to PADCEV was 3.7 months (range: 0.03 to 7.6 months) and the median number of cycles of PADCEV was 6 (range: 1, 6) in the adjuvant phase. Across the combined neoadjuvant and adjuvant phases (n=167), the median number of cycles of PADCEV was 5 (range: 1, 9) out of a planned 9 cycles.

Table 5 summarizes the most common (≥20%) adverse reactions in EV-303.

Table 5. Adverse Reactions ≥20% (All Grades) in Patients Treated with PADCEV in Combination with Intravenous Pembrolizumab in EV-303

Adverse Reaction	PADCEV in combination with intravenous pembrolizumab before and after RC with PLND n=167		RC with PLND alone n=159	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Skin and subcutaneous tissue disorders				
Rash[1]	54	7	1.3	0
Pruritus	47	3	0	0
Alopecia	35	0.6	0	0
General disorders and administration site conditions				
Fatigue[1]	47	4.2	6	0.6
Nervous system disorders				
Peripheral neuropathy[1]	39	3	1.9	0
Dysgeusia[1]	35	0	0	0
Gastrointestinal disorders				
Diarrhea[1]	34	5	3.1	1.3
Constipation	28	1.8	8	0
Nausea	26	1.2	8	0.6
Metabolism and nutrition disorders				
Decreased appetite	28	0.6	1.9	0
Infections and infestations				
Urinary tract infection	24	12	13	11
Eye disorders				
Dry eye[1]	21	0	0	0
Investigations				
Decreased weight	20	0	3.1	0

1. Includes: multiple terms.

Clinically relevant adverse reactions (<20%) include dry skin (15%), hypothyroidism (14%), vomiting (9%), pneumonitis/ILD (4.2%), skin hyperpigmentation (3%), infusion site extravasation (1.2%), and myasthenia gravis and myositis (0.6% each).

Table 6. Selected Laboratory Abnormalities Reported in ≥20% (All Grades) of Patients Treated with PADCEV in Combination with Intravenous Pembrolizumab in EV-303

Laboratory Abnormality	PADCEV in combination with intravenous pembrolizumab before and after RC with PLND		RC with PLND alone	
	All Grades[1] %	Grade 3-4[1] %	All Grades[1] %	Grade 3-4[1] %
Chemistry				
Increased glucose	72	12	24	1.7
Increased aspartate aminotransferase	55	6	11	1.8
Increased alanine aminotransferase	53	4.8	13	0.9
Increased creatinine	47	8	31	2.5
Decreased sodium	44	13	18	7
Increased potassium	39	7	20	6
Decreased phosphate	26	6	1.8	0
Hematology				
Decreased hemoglobin	60	13	48	8
Decreased lymphocytes	40	8	17	1.7

1. The denominator used to calculate the rate of PADCEV in combination with intravenous pembrolizumab was 167 and the denominator used to calculate the rate for RC and PLND alone varied from 110 to 121 based on the number of patients with a baseline value and at least one post-treatment value.

Neoadjuvant Phase of EV-303

A total of 167 patients received at least one dose of PADCEV in combination with intravenous pembrolizumab as neoadjuvant treatment before receiving RC.

In the neoadjuvant phase, serious adverse reactions occurred in 27% of patients receiving PADCEV in combination with intravenous pembrolizumab. The most frequent (≥2%) serious adverse reactions were urinary tract infection (3.6%) and hematuria (2.4%). Fatal adverse reactions occurred in 1.2% of patients including myasthenia gravis and toxic epidermal necrolysis (0.6% each). Additional fatal adverse reactions were reported in 2.7% of patients in the post-surgery phase before adjuvant treatment started, including sepsis and intestinal obstruction (1.4% each).

Adverse reactions leading to discontinuation of PADCEV in the neoadjuvant phase occurred in 22% of patients. The most common adverse reactions (≥1%) leading to discontinuation of PADCEV were rash (4.8%), peripheral neuropathy (2.4%), and diarrhea, dysgeusia, fatigue, pruritus, and toxic epidermal necrolysis (1.2% each).

Adverse reactions leading to dose interruption of PADCEV in the neoadjuvant phase occurred in 29% of patients. The most common adverse reactions (≥2%) leading to dose interruption of PADCEV were rash (8%), neutropenia (3.6%), hyperglycemia (3%), and fatigue and peripheral neuropathy (2.4% each).

Adverse reactions leading to dose reduction of PADCEV in the neoadjuvant phase occurred in 13% of patients. The most common adverse reactions (≥1%) leading to dose reduction of PADCEV were rash (4.8%), pruritus (1.8%), and peripheral neuropathy, increase alanine aminotransferase, increased aspartate aminotransferase, decreased appetite, fatigue, neutropenia, and decreased weight (1.2% each).

Of the 167 patients in the PADCEV in combination with intravenous pembrolizumab arm who received neoadjuvant treatment, 7 (4.2%) patients did not receive surgery due to adverse reactions. The adverse reactions that led to cancellation of surgery were acute myocardial infarction, bile duct cancer, colon cancer, respiratory distress, urinary tract infection and the deaths due to myasthenia gravis and toxic epidermal necrolysis (0.6% each).

Of the 146 patients who received neoadjuvant treatment with PADCEV in combination with intravenous pembrolizumab and underwent RC, 6 (4.1%) patients experienced delay of surgery (defined as time from last neoadjuvant treatment to surgery exceeding 8 weeks) due to adverse reactions.

Adjuvant Phase of EV-303

Patients who did not proceed to surgery were ineligible for adjuvant treatment. Of the 149 patients who underwent surgery, 100 patients received adjuvant treatment with PADCEV in combination with intravenous pembrolizumab. Of the 49 patients who did not receive adjuvant treatment, discontinuation of treatment with PADCEV in combination with intravenous pembrolizumab prior to the adjuvant phase was due to an adverse event in 21 patients.

In the adjuvant phase, serious adverse reactions occurred in 43% of patients receiving PADCEV in combination with intravenous pembrolizumab. The most frequent (≥2%) serious adverse reactions were urinary tract infection (8%), acute kidney injury and pyelonephritis (5% each), urosepsis (4%), and hypokalemia, intestinal obstruction, and sepsis (2% each). Fatal adverse reactions occurred in 7% of patients, including urosepsis, hemorrhage intracranial, death, myocardial infarction, multiple organ dysfunction syndrome, and pneumonia pseudomonal (1% each).

Adverse reactions leading to discontinuation of PADCEV in the adjuvant phase occurred in 26% of patients. The most common adverse reactions (≥2%) leading to discontinuation of PADCEV were peripheral neuropathy (5%) and rash (4%).

Adverse reactions leading to dose interruption of PADCEV in the adjuvant phase occurred in 36% of patients. The most common adverse reactions (≥2%) leading to dose interruption of PADCEV were rash (6%), diarrhea and urinary tract infection (5% each), fatigue (4%), pruritus (3%), and peripheral neuropathy and pyelonephritis (2% each).

Adverse reactions leading to dose reduction of PADCEV in the adjuvant phase occurred in 7% of patients. The most common adverse reaction (≥2%) leading to dose reduction of PADCEV was weight decreased (2%).

Previously Untreated Locally Advanced or mUC

EV-302

The safety of PADCEV in combination with intravenous pembrolizumab was evaluated in an open-label, randomized, multicenter trial (EV-302) in patients with locally advanced or mUC. Patients received either PADCEV 1.25 mg/kg and pembrolizumab (n=440) or gemcitabine and platinum chemotherapy (either cisplatin or carboplatin) (n=433). Among patients who received PADCEV and pembrolizumab, the median duration of exposure for PADCEV was 7 months (range: 0.3 to 31.9 months).

Serious adverse reactions occurred in 50% of patients treated with PADCEV in combination with intravenous pembrolizumab. The most common serious adverse reactions (≥2%) were rash (6%), acute kidney injury (5%), pneumonitis/ILD (4.5%), urinary tract infection (3.6%), diarrhea (3.2%), pneumonia (2.3%), pyrexia (2%), and hyperglycemia (2%).

Fatal adverse reactions occurred in 3.9% of patients treated with PADCEV in combination with intravenous pembrolizumab including acute respiratory failure (0.7%), pneumonia (0.5%), and pneumonitis/ILD (0.2%).

Adverse reactions leading to discontinuation of PADCEV occurred in 35% of patients. The most common adverse reactions (≥2%) leading to discontinuation of PADCEV were peripheral neuropathy (15%), rash (4.1%), and pneumonitis/ILD (2.3%).

Adverse reactions leading to dose interruption of PADCEV occurred in 73% of patients. The most common adverse reactions (≥2%) leading to dose interruption of PADCEV were peripheral neuropathy (22%), rash (16%), COVID-19 (10%), diarrhea (5%), pneumonitis/ILD (4.8%), fatigue (3.9%), hyperglycemia (3.6%), increased alanine aminotransferase (3%), and pruritus (2.5%).

Adverse reactions leading to dose reduction of PADCEV occurred in 42% of patients. The most common adverse reactions (≥2%) leading to dose reduction of PADCEV were rash (16%), peripheral neuropathy (13%), and fatigue (2.7%).

Table 7 summarizes the most common (≥15%) adverse reactions in EV-302.

Table 7. Adverse Reactions ≥15% (All Grades) in Patients Treated with PADCEV in Combination with Intravenous Pembrolizumab in EV-302

Adverse Reaction	PADCEV in combination with intravenous pembrolizumab n=440		Chemotherapy n=433	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Skin and subcutaneous tissue disorders				
Rash[1]	68	15	15	0
Pruritus	41	1.1	7	0
Alopecia	35	0.5	8	0.2
Dry skin	17	0.2	1	0
General disorders and administration site conditions				
Fatigue[1]	51	6	57	7
Pyrexia	18	0.7	16	1.2
Nervous system disorders				
Peripheral neuropathy[1]	67	8	14	0
Dysgeusia	21	0	9	0
Metabolism and nutrition disorders				
Decreased appetite	33	1.8	26	1.8
Gastrointestinal disorders				
Diarrhea	38	4.5	16	1.4
Nausea	26	1.6	41	2.8
Constipation	26	0	34	0.7
Investigations				
Decreased weight	33	3.6	9	0.2
Eye disorders				
Dry eye[1]	24	0	2.1	0
Infections and infestations				
Urinary tract infection	21	5	19	8

1. Includes: multiple terms.

Clinically relevant adverse reactions (<15%) include vomiting (12%), pneumonitis/ILD and hypothyroidism (10% each), blurred vision and skin hyperpigmentation (6% each), infusion site extravasation (1.8%), and myositis (0.5%).

Table 8. Selected Laboratory Abnormalities Reported in ≥15% (All Grades) of Patients Treated with PADCEV in Combination with Intravenous Pembrolizumab in EV-302

Laboratory Abnormality	PADCEV in combination with intravenous pembrolizumab		Chemotherapy	
	All Grades[1] %	Grade 3-4[1] %	All Grades[1] %	Grade 3-4[1] %
Chemistry				
Increased aspartate aminotransferase	75	5	39	3
Increased creatinine	71	3	68	3
Increased glucose	66	14	54	5
Increased alanine aminotransferase	59	5	49	3
Decreased sodium	46	13	47	13
Decreased phosphate	44	9	36	9
Decreased albumin	39	2	35	0.5
Decreased potassium	26	5	16	3
Increased potassium	24	1	36	4
Increased calcium	21	1	14	0.2
Hematology				
Decreased lymphocytes	58	15	59	17
Decreased hemoglobin	53	7	89	33
Decreased neutrophils	30	9	80	50

1. The denominator used to calculate the rate varied from 407 to 439 based on the number of patients with a baseline value and at least one post-treatment value.

Previously Untreated Cisplatin-Ineligible Patients with Locally Advanced or mUC

EV-103

The safety of PADCEV was evaluated in combination with intravenous pembrolizumab in a multi cohort trial (EV-103) in 121 patients with locally advanced or mUC who were not eligible for cisplatin-containing chemotherapy and received at least one dose of PADCEV 1.25 mg/kg and pembrolizumab *[see Clinical Studies (14)]*. The median duration of exposure to PADCEV was 7 months (range: 0.6 to 33 months).

Serious adverse reactions occurred in 50% of patients treated with PADCEV in combination with intravenous pembrolizumab. The most common serious adverse reactions (≥2%) were acute kidney injury (7%), urinary tract infection (7%), urosepsis (5%), sepsis (3.3%), pneumonia (3.3%), hematuria (3.3%), pneumonitis/ILD (3.3%), urinary retention (2.5%), diarrhea (2.5%), myasthenia gravis (2.5%), myositis (2.5%), anemia (2.5%), and hypotension (2.5%).

Fatal adverse reactions occurred in 5% of patients treated with PADCEV in combination with intravenous pembrolizumab including sepsis (1.6%), bullous dermatitis (0.8%), myasthenia gravis (0.8%), and pneumonitis/ILD (0.8%).

Adverse reactions leading to discontinuation of PADCEV occurred in 36% of patients. The most common adverse reactions (≥2%) leading to discontinuation of PADCEV were peripheral neuropathy (20%) and rash (6%).

Adverse reactions leading to dose interruption of PADCEV occurred in 69% of patients. The most common adverse reactions (≥2%) leading to dose interruption of PADCEV were peripheral neuropathy (18%), rash (12%), increased lipase (6%), pneumonitis/ILD (6%), diarrhea (4.1%), acute kidney injury (3.3%), increased alanine aminotransferase (3.3%), fatigue (3.3%), neutropenia (3.3%), urinary tract infection (3.3%), increased amylase (2.5%), anemia (2.5%), COVID-19 (2.5%), hyperglycemia (2.5%), and hypotension (2.5%).

Adverse reactions leading to dose reduction of PADCEV occurred in 45% of patients. The most common adverse reactions (≥2%) leading to dose reduction of PADCEV were peripheral neuropathy (17%), rash (12%), fatigue (5%), neutropenia (5%), and diarrhea (4.1%).

Table 9 summarizes the most common (≥20%) adverse reactions in EV-103.

Table 9. Adverse Reactions ≥20% (All Grades) in Patients Treated with PADCEV in Combination with Intravenous Pembrolizumab in EV-103

Adverse Reaction	PADCEV in combination with intravenous pembrolizumab n=121	
	All Grades %	Grade 3-4 %
Skin and subcutaneous tissue disorders		
Rash[1]	71	21
Alopecia	52	0
Pruritus	40	3.3
Dry skin	21	0.8
Nervous system disorders		
Peripheral neuropathy[1]	65	3.3
Dysgeusia	35	0
Dizziness	23	0
General disorders and administration site conditions		
Fatigue	60	11
Peripheral edema	26	0
Investigations		
Decreased weight	48	5
Gastrointestinal disorders		
Diarrhea	45	7
Nausea	36	0.8
Constipation	27	0
Metabolism and nutrition disorders		
Decreased appetite	38	0.8
Infections and infestations		
Urinary tract infection	30	12
Eye disorders		
Dry eye	25	0
Musculoskeletal and connective tissue disorders		
Arthralgia	23	1.7

1. Includes: multiple terms.

Clinically relevant adverse reactions (<20%) include vomiting (20%), pyrexia (18%), hypothyroidism (11%), pneumonitis/ILD (10%), skin hyperpigmentation (8%), myasthenia gravis (2.5%), myositis (3.3%), and infusion site extravasation (0.8%).

Table 10. Selected Laboratory Abnormalities ≥20% (All Grades) in Patients Treated with PADCEV in Combination with Intravenous Pembrolizumab in EV-103

Laboratory Abnormality	PADCEV in combination with intravenous pembrolizumab	
	All Grades[1] %	Grade 3-4[1] %
Chemistry		
Increased glucose	74	13
Increased aspartate aminotransferase	73	9
Increased creatinine	69	3.3
Decreased sodium	60	19
Increased alanine aminotransferase	60	7
Increased lipase	59	32
Decreased albumin	59	4.2
Decreased phosphate	51	15
Decreased potassium	35	8
Increased potassium	27	1.7
Increased calcium	27	4.2
Hematology		
Decreased hemoglobin	69	15
Decreased lymphocytes	64	17
Decreased neutrophils	32	12

1. The denominator used to calculate the rate varied from 114 to 121 based on the number of patients with a baseline value and at least one post-treatment value.

Previously Treated Locally Advanced or mUC

EV-301

The safety of PADCEV was evaluated as a single agent in EV-301 in patients with locally advanced or mUC (n=296) who received at least one dose of PADCEV 1.25 mg/kg and who were previously treated with a PD-1 or PD-L1 inhibitor and a platinum-based chemotherapy *[see Clinical Studies (14)]*. Routine ophthalmologic exams were not conducted in EV-301. The median duration of exposure to PADCEV was 5 months (range: 0.5 to 19 months).

Serious adverse reactions occurred in 47% of patients treated with PADCEV. The most common serious adverse reactions (≥2%) were urinary tract infection, acute kidney injury (7% each), and pneumonia (5%). Fatal adverse reactions occurred in 3% of patients, including multiorgan dysfunction (1%), hepatic dysfunction, septic shock, hyperglycemia, pneumonitis/ILD, and pelvic abscess (0.3% each).

Adverse reactions leading to discontinuation occurred in 17% of patients; the most common adverse reactions (≥2%) leading to discontinuation were peripheral neuropathy (5%) and rash (4%).

Adverse reactions leading to dose interruption occurred in 61% of patients; the most common adverse reactions (≥4%) leading to dose interruption were peripheral neuropathy (23%), rash (11%), and fatigue (9%).

Adverse reactions leading to dose reduction occurred in 34% of patients; the most common adverse reactions (≥2%) leading to dose reduction were peripheral neuropathy (10%), rash (8%), decreased appetite (3%), and fatigue (3%).

Table 11 summarizes the most common (⩾15%) adverse reactions in EV-301.

Table 11. Adverse Reactions (≥15%) in Patients Treated with PADCEV in EV-301

Adverse Reaction	PADCEV n=296		Chemotherapy n=291	
	All Grades %	Grade 3-4 %	All Grades %	Grade 3-4 %
Skin and subcutaneous tissue disorders				
Rash[1]	54	14	20	0.3
Alopecia	47	0	38	0
Pruritus	34	2	7	0
Dry skin	17	0	4	0
General disorders and administration site conditions				
Fatigue[1]	50	9	40	7
Pyrexia[1]	22	2	14	0
Nervous system disorders				
Peripheral neuropathy[1]	50	5	34	3
Dysgeusia[1]	26	0	8	0
Metabolism and nutrition disorders				
Decreased appetite	41	5	27	2
Gastrointestinal disorders				
Diarrhea[1]	35	4	23	2
Nausea	30	1	25	2
Constipation	28	1	25	2
Abdominal Pain[1]	20	1	14	3
Musculoskeletal and connective tissue disorders				
Musculoskeletal Pain[1]	25	2	35	5
Eye Disorders				
Dry eye[1]	24	0.7	6	0.3
Infections and infestations				
Urinary Tract Infection[1]	17	6	13	3
Vascular disorders				
Hemorrhage[1]	17	3	13	2
Investigations				
Decreased weight	16	0.3	7	0

1. Includes: multiple terms.

Clinically relevant adverse reactions (<15%) include vomiting (14%), increased aspartate aminotransferase (12%), hyperglycemia (10%), increased alanine aminotransferase (9%), skin hyperpigmentation (8%), pneumonitis/ILD (3%), and infusion site extravasation (0.7%).

Table 12. Selected Laboratory Abnormalities Reported in ≥15% (Grades 2-4) or ≥5% (Grade 3-4) of Patients Treated with PADCEV in EV-301

Laboratory Abnormality	PADCEV[1]		Chemotherapy[1]	
	Grades 2-4 %	Grade 3-4 %	Grades 2-4 %	Grade 3-4 %
Hematology				
Decreased lymphocytes	41	14	34	18
Decreased hemoglobin	28	4	42	14
Decreased neutrophils	27	12	25	17
Chemistry				
Decreased phosphate	39	8	24	6
Increased glucose (non-fasting)	33	9	27	6
Increased creatinine	18	2	13	0
Decreased potassium	16	2	7	3
Increased lipase	13	8	7	4
Decreased sodium	8	8	5	5

1. The denominator used to calculate the rate varied from 262 to 287 based on the number of patients with a baseline value and at least one post-treatment value.

EV-201, Cohort 1

The safety of PADCEV was evaluated as a single agent in EV-201, Cohort 1 in patients (n=125) with locally advanced or mUC who had received prior treatment with a PD-1 or PD-L1 inhibitor and platinum-based chemotherapy *[see Clinical Studies (14)]*. Patients received PADCEV 1.25 mg/kg on Days 1, 8, and 15 of a 28-day cycle until disease progression or unacceptable toxicity. The median duration of exposure to PADCEV was 4.6 months (range: 0.5 to 15.6 months).

Serious adverse reactions occurred in 46% of patients treated with PADCEV. The most common serious adverse reactions (≥3%) were urinary tract infection (6%), cellulitis (5%), febrile neutropenia (4%), diarrhea (4%), sepsis (3%), acute kidney injury (3%), dyspnea (3%), and rash (3%). Fatal adverse reactions occurred in 3.2% of patients, including acute respiratory failure, aspiration pneumonia, cardiac disorder, sepsis, and pneumonitis/ILD (each 0.8%).

Adverse reactions leading to discontinuation occurred in 16% of patients; the most common adverse reaction leading to discontinuation was peripheral neuropathy (6%).

Adverse reactions leading to dose interruption occurred in 64% of patients; the most common adverse reactions leading to dose interruption were peripheral neuropathy (18%), rash (9%), and fatigue (6%).

Adverse reactions leading to dose reduction occurred in 34% of patients; the most common adverse reactions leading to dose reduction were peripheral neuropathy (12%), rash (6%), and fatigue (4%).

Table 13 summarizes the All Grades and Grades 3-4 adverse reactions reported in patients in EV-201, Cohort 1.

Table 13. Adverse Reactions Reported in ≥15% (All Grades) or ≥5% (Grade 3-4) of Patients Treated with PADCEV in EV-201 Cohort 1

Adverse Reaction	PADCEV n=125	
	All Grades %	Grade 3-4 %
General disorders and administration site conditions		
Fatigue[1]	56	6
Nervous system disorders		
Peripheral neuropathy[1]	56	4
Dysgeusia	42	0
Metabolism and nutrition disorders		
Decreased appetite	52	2
Skin and subcutaneous tissue disorders		
Rash[1]	52	13
Alopecia	50	0
Dry skin	26	0
Pruritus[1]	26	2
Gastrointestinal disorders		
Nausea	45	3
Diarrhea[1]	42	6
Vomiting	18	2
Eye disorders		
Dry eye[1]	40	0

1. Includes: multiple terms.

Clinically relevant adverse reactions (<15%) include skin hyperpigmentation (14%), herpes zoster (3%), pneumonitis/ILD (2%), and infusion site extravasation (2%).

Table 14. Selected Laboratory Abnormalities Reported in ≥15% (Grades 2-4) or ≥5% (Grade 3-4) of Patients Treated with PADCEV in EV-201, Cohort 1

Laboratory Abnormality	PADCEV	
	Grades 2-4[1] %	Grade 3-4[1] %
Hematology		
Decreased hemoglobin	34	10
Decreased lymphocytes	32	10
Decreased neutrophils	14	5
Chemistry		
Decreased phosphate	34	10
Increased glucose (non-fasting)	27	8
Increased creatinine	20	2
Decreased potassium	19[2]	1
Increased lipase	14	9
Decreased sodium	8	8
Increased urate	7	7

1. Denominator for each laboratory parameter is based on the number of patients with a baseline and post-treatment laboratory value available for 121 or 122 patients.
2. Includes Grade 1 (potassium 3.0-3.5 mmol/L) – Grade 4.

EV-201, Cohort 2

The safety of PADCEV was evaluated as a single agent in EV-201, Cohort 2 in patients with locally advanced or mUC (n=89) who received at least one dose of PADCEV 1.25 mg/kg and had prior treatment with a PD-1 or PD-L1 inhibitor and were not eligible for cisplatin-based chemotherapy. The median duration of exposure was 5.98 months (range: 0.3 to 24.6 months).

Serious adverse reactions occurred in 39% of patients treated with PADCEV. The most common serious adverse reactions (≥3%) were pneumonia, sepsis, and diarrhea (5% each). Fatal adverse reactions occurred in 8% of patients, including acute kidney injury (2.2%), metabolic acidosis, sepsis, multiorgan dysfunction, pneumonia, and pneumonitis/ILD (1.1% each).

Adverse reactions leading to discontinuation occurred in 20% of patients; the most common adverse reaction (≥2%) leading to discontinuation was peripheral neuropathy (7%).

Adverse reactions leading to dose interruption occurred in 60% of patients; the most common adverse reactions (≥3%) leading to dose interruption were peripheral neuropathy (19%), rash (9%), fatigue (8%), diarrhea (5%), increased aspartate aminotransferase (3%), and hyperglycemia (3%).

Adverse reactions leading to dose reduction occurred in 49% of patients; the most common adverse reactions (≥3%) leading to dose reduction were peripheral neuropathy (19%), rash (11%), and fatigue (7%).

Table 15 summarizes the All Grades and Grades 3-4 adverse reactions reported in patients in EV-201, Cohort 2.

Table 15. Adverse Reactions ≥15% (All Grades) or ≥5% (Grades 3-4) in Patients Treated with PADCEV in EV-201, Cohort 2

Adverse Reaction	PADCEV n=89	
	All Grades (%)	Grades 3-4 (%)
Skin and subcutaneous tissue disorders		
Rash[1]	66	17
Alopecia	53	0
Pruritus	35	3
Dry skin	19	1
Nervous system disorders		
Peripheral neuropathy[1]	58	8
Dysgeusia[1]	29	0
General disorders and administration site conditions		
Fatigue[1]	48	11
Metabolism and nutrition disorders		
Decreased appetite	40	6
Hyperglycemia	16	9
Gastrointestinal disorders		
Diarrhea[1]	36	8
Nausea	30	1
Investigations		
Decreased weight	35	1
Eye disorders		
Dry eye[1]	30	0

1. Includes: multiple terms.

Clinically relevant adverse reactions (<15%) include vomiting (13%), increased aspartate aminotransferase (12%), increased lipase (11%), increased alanine aminotransferase (10%), skin hyperpigmentation (4%), pneumonitis/ILD (4%), and infusion site extravasation (1%).

Table 16. Selected Laboratory Abnormalities Reported in ≥15% (Grades 2-4) or ≥5% (Grades 3-4) of Patients Treated with PADCEV in EV-201, Cohort 2

Laboratory Abnormality	PADCEV n=88[1]	
	Grades 2-4[1] %	Grade 3-4[1] %
Hematology		
Decreased lymphocytes	43	15
Decreased hemoglobin	34	5
Decreased neutrophils	20	9
Chemistry		
Increased glucose (non-fasting)	36	13
Decreased phosphate	25	7
Increased creatinine	23	3
Increased lipase	18	11
Increased urate	9	9
Increased potassium	8	6
Decreased sodium	7	7

1. Based on the number of patients with a baseline value and at least one post-treatment value.

6.2 Post Marketing Experience

The following adverse reactions have been identified during post-approval use of PADCEV. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Skin and subcutaneous tissue disorders: Epidermal necrosis, Stevens-Johnson syndrome, and toxic epidermal necrolysis *[see Warnings and Precautions (5.1)]*.

7 DRUG INTERACTIONS

7.1 Effects of Other Drugs on PADCEV

Dual P-gp and Strong CYP3A4 Inhibitors

Concomitant use with dual P-gp and strong CYP3A4 inhibitors may increase unconjugated MMAE exposure *[see Clinical Pharmacology (12.3)]*, which may increase the incidence or severity of PADCEV toxicities. Closely monitor patients for signs of toxicity when PADCEV is given concomitantly with dual P-gp and strong CYP3A4 inhibitors.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on the mechanism of action and findings in animals, PADCEV can cause fetal harm when administered to a pregnant woman *[see Clinical Pharmacology (12.1)]*. There are no available human data on PADCEV use in pregnant women to inform a drug-associated risk. In an animal reproduction study, administration of enfortumab vedotin-ejfv to pregnant rats during organogenesis caused maternal toxicity, embryo-fetal lethality, structural malformations, and skeletal anomalies at maternal exposures similar to the exposures at the recommended human dose of 1.25 mg/kg *(see Data)*. Advise patients of the potential risk to the fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data

In a rat pilot embryo-fetal development study, administration of enfortumab vedotin-ejfv on gestation day 6 and 13 during the period of organogenesis resulted in a complete litter loss in all pregnant rats at the maternally toxic dose of 5 mg/kg (approximately 3 times the exposure at the recommended human dose). A dose of 2 mg/kg (similar to the exposure at the recommended human dose) resulted in maternal toxicity, embryo-fetal lethality, and structural malformations that included gastroschisis, malrotated hindlimb, absent forepaw, malpositioned internal organs, and fused cervical arch. Additionally, skeletal anomalies (asymmetric, fused, incompletely ossified, and misshapen sternebrae, misshapen cervical arch, and unilateral ossification of the thoracic centra) and decreased fetal weight were observed.

8.2 Lactation

Risk Summary

There are no data on the presence of enfortumab vedotin-ejfv in human milk, the effects on the breastfed child, or the effects on milk production. Because of the potential for serious adverse reactions in a breastfed child, advise lactating women not to breastfeed during treatment with PADCEV and for 3 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify pregnancy status in females of reproductive potential prior to initiating PADCEV treatment *[see Use in Specific Populations (8.1)]*.

Contraception

Females

PADCEV can cause fetal harm when administered to a pregnant woman *[see Use in Specific Populations (8.1)]*. Advise females of reproductive potential to use effective contraception during treatment with PADCEV and for 2 months after the last dose.

Males

Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose.

Infertility

Females

Based on findings in animal studies with MMAE-containing antibody-drug conjugates (ADCs), PADCEV may impair female fertility. The effect on fertility is reversible *[see Nonclinical Toxicology (13.1)]*.

Males

Based on findings from animal studies, PADCEV may impair male fertility *[see Nonclinical Toxicology (13.1)]*.

8.4 Pediatric Use

Safety and effectiveness of PADCEV in pediatric patients have not been established.

8.5 Geriatric Use

Of the 167 patients treated with PADCEV in combination with intravenous pembrolizumab for the treatment of MIBC, 37% (n=61) were 65-74 years and 46% (n=77) were 75 years or older. Of the 564 patients treated with PADCEV in combination with intravenous pembrolizumab for the treatment of locally advanced or mUC, 44% (n=247) were 65-74 years and 26% (n=144) were 75 years or older. Of the 720 patients treated with PADCEV as a single agent in clinical trials, 39% (n=282) were 65-74 years and 24% (n=170) were 75 years or older. No overall differences in effectiveness were observed between patients 65 years of age or older and younger patients.

Patients 75 years of age or older treated with PADCEV in combination with intravenous pembrolizumab for the treatment of MIBC experienced a higher incidence of fatal adverse reactions than younger patients. The incidence of fatal adverse reactions was 4% in patients younger than 75 and 12% in patients 75 years or older.

Patients 75 years of age or older treated with PADCEV in combination with intravenous pembrolizumab for the treatment of locally advanced or mUC experienced a higher incidence of fatal adverse reactions than younger patients. The incidence of fatal adverse reactions was 4% in patients younger than 75 and 7% in patients 75 years or older.

Patients 75 years of age or older treated with PADCEV as a single agent experienced a higher incidence of fatal adverse reactions than younger patients. The incidence of fatal adverse reactions was 6% in patients younger than 75 years, and 11% in patients 75 years or older.

No significant difference was observed in the pharmacokinetics of PADCEV between patients 65 years and older and younger patients *[see Clinical Pharmacology (12.3)]*.

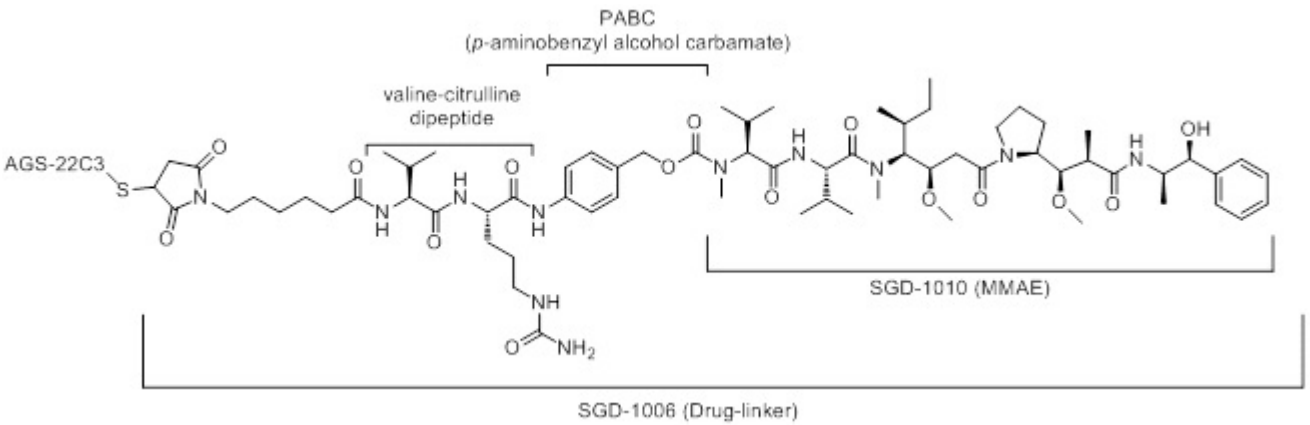
8.6 Hepatic Impairment

Avoid the use of PADCEV in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST). PADCEV has only been studied in a limited number of patients with moderate or severe hepatic impairment *[see Clinical Pharmacology (12.3)]*. In another ADC that contains MMAE, the frequency of ≥ Grade 3 adverse reactions and deaths was greater in patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment compared to patients with normal hepatic function.

11 DESCRIPTION

Enfortumab vedotin-ejfv is a Nectin-4 directed antibody-drug conjugate (ADC) comprised of a fully human anti-Nectin-4 IgG1 kappa monoclonal antibody (AGS-22C3) conjugated to the small molecule microtubule disrupting agent, monomethyl auristatin E (MMAE) via a protease-cleavable maleimidocaproyl valine-citrulline (vc) linker (SGD-1006). Conjugation takes place on cysteine residues that comprise the interchain disulfide bonds of the antibody to yield a product with a drug-to-antibody ratio of approximately 3.8:1. The molecular weight is approximately 152 kDa.

Figure 1. Structural Formula



Approximately 4 molecules of MMAE are attached to each antibody molecule. Enfortumab vedotin-ejfv is produced by chemical conjugation of the antibody and small molecule components. The antibody is produced by mammalian (Chinese hamster ovary) cells and the small molecule components are produced by chemical synthesis.

PADCEV (enfortumab vedotin-ejfv) for injection is provided as a sterile, preservative-free, white to off-white lyophilized powder in single-dose vials for intravenous use. PADCEV is supplied as a 20 mg per vial and a 30 mg per vial and requires reconstitution with Sterile Water for Injection, USP, (2.3 mL and 3.3 mL, respectively) resulting in a clear to slightly opalescent, colorless to slightly yellow solution with a final concentration of 10 mg/mL *[see Dosage and Administration (2.3)]*. After reconstitution, each vial allows the withdrawal of 2 mL (20 mg) and 3 mL (30 mg). Each mL of reconstituted solution contains 10 mg of enfortumab vedotin-ejfv, histidine (1.4 mg), histidine hydrochloride monohydrate (2.31 mg), polysorbate 20 (0.2 mg), and trehalose dihydrate (55 mg) with a pH of 6.0.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Enfortumab vedotin-ejfv is an ADC. The antibody is a human IgG1 kappa directed against Nectin-4, an adhesion protein located on the surface of cells. The small molecule, MMAE, is a microtubule-disrupting agent, attached to the antibody via a protease-cleavable linker. Nonclinical data suggest that the anticancer activity of enfortumab vedotin-ejfv is due to the binding of the ADC to Nectin-4-expressing cells, followed by internalization of the ADC-Nectin-4 complex, and the release of MMAE via proteolytic cleavage. Release of MMAE disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptosis. The combination of enfortumab vedotin-ejfv with a PD-1 blocking antibody resulted in up-regulation of immune function and increased anti-tumor activity in syngeneic mouse tumor models expressing Nectin-4.

12.2 Pharmacodynamics

In an exposure-response analysis for safety, higher enfortumab vedotin-ejfv exposure was associated with higher incidence of some adverse reactions (e.g., Grade ≥2 peripheral neuropathy, Grade ≥3 hyperglycemia). The exposure-response relationship for efficacy has not been fully characterized.

Cardiac Electrophysiology

At the recommended dose, PADCEV had no large QTc prolongation (>20 msec).

12.3 Pharmacokinetics

Enfortumab vedotin-ejfv (ADC) pharmacokinetics were characterized after single and multiple doses in patients with solid tumors.

The pharmacokinetics of the ADC and unconjugated MMAE were consistent when assessed following PADCEV administration as a single agent and in combination with intravenous pembrolizumab after 1 treatment cycle.

The exposure parameters of the ADC and unconjugated MMAE (the cytotoxic component of enfortumab vedotin-ejfv) are summarized in Table 17 below. Peak ADC concentrations were observed near the end of intravenous infusion while peak unconjugated MMAE concentrations were observed approximately 2 days after PADCEV dosing. Minimal accumulation of the ADC and unconjugated MMAE was observed following repeat administration of PADCEV in patients. Steady-state concentrations of the ADC were reached after 1 treatment cycle for the ADC as a single agent and in combination with intravenous pembrolizumab.

Table 17. Exposure Parameters of the ADC and Unconjugated MMAE after First Treatment Cycle of 1.25 mg/kg of PADCEV Dose of Days 1, 8, and 15

Parameter	ADC Mean (± SD)	Unconjugated MMAE Mean (± SD)
C_{max}	28 (6.1) µg/mL	5.5 (3.0) ng/mL
$AUC_{0\text{-}28d}$	110 (26) µg·d/mL	85 (50) ng·d/mL
$C_{trough,0\text{-}28d}$	0.31 (0.18) µg/mL	0.81 (0.88) ng/mL

C_{max} = maximum concentration, $AUC_{0\text{-}28d}$ = area under the concentration-time curve from time zero to 28 days, $C_{trough,0\text{-}28d}$ = pre-dose concentration on day 28.

Distribution

The estimated mean steady-state volume of distribution of the ADC was 12.8 L following administration of PADCEV. *In vitro*, plasma protein binding of unconjugated MMAE ranged from 68% to 82%.

Elimination

The ADC and unconjugated MMAE exhibited multi-exponential declines with an elimination half-life of 3.6 days and 2.6 days, respectively. The mean clearance (CL) of the ADC and unconjugated MMAE was 0.11 L/h and 2.11 L/h, respectively. Elimination of unconjugated MMAE appeared to be limited by its rate of release from the ADC.

Metabolism

Catabolism of the ADC has not been studied in humans; however, it is expected to undergo catabolism to small peptides, amino acids, unconjugated MMAE, and unconjugated MMAE-related catabolites. The ADC releases MMAE via proteolytic cleavage, and unconjugated MMAE is primarily metabolized by CYP3A4 *in vitro*.

Excretion

The excretion of the ADC is not fully characterized. Following a single-dose of another ADC that contains unconjugated MMAE, 17% of the total unconjugated MMAE administered was recovered in feces and 6% in urine over a 1-week period, primarily as unchanged form. A similar excretion profile of unconjugated MMAE is expected after PADCEV administration.

Specific Populations

No clinically significant differences in the pharmacokinetics of the ADC or unconjugated MMAE were identified based on age (24 to 90 years), sex, race (White, Asian, or Black), renal impairment, and mild hepatic impairment (total bilirubin of 1 to 1.5 × ULN and any AST, or total bilirubin ≤ULN and AST >ULN). The effect of end-stage renal disease with or without dialysis and moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) on the pharmacokinetics of the ADC or unconjugated MMAE is unknown.

Drug Interaction Trials

No clinical trials evaluating the drug-drug interaction potential of the ADC have been conducted.

Physiologically Based Pharmacokinetic (PBPK) Modeling Predictions:

Dual P-gp and Strong CYP3A4 Inhibitor: Concomitant use of PADCEV with ketoconazole (a dual P-gp and strong CYP3A4 inhibitor) is predicted to increase unconjugated MMAE C_{max} by 15% and AUC by 38%.

Dual P-gp and Strong CYP3A4 Inducer: Concomitant use of PADCEV with rifampin (a dual P-gp and strong CYP3A4 inducer) is predicted to decrease unconjugated MMAE C_{max} by 28% and AUC by 53%.

Sensitive CYP3A Substrates: Concomitant use of PADCEV is predicted not to affect exposure to midazolam (a sensitive CYP3A substrate).

In Vitro Studies

Transporter Systems: MMAE is a substrate of P-glycoprotein (P-gp) and is not an inhibitor of P-gp.

12.6 Immunogenicity

The observed incidence of anti-drug antibody (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of PADCEV or of other enfortumab vedotin products.

ADA was evaluated during the treatment periods (up to 5.5 years) in nine clinical studies of PADCEV as a single agent or in combination with intravenous pembrolizumab at the approved recommended dosages. Anti-enfortumab vedotin-ejfv antibodies developed in:

- 3.7% (25/684) of patients who received PADCEV as a single agent.
- 1.3% (2/156) of patients who received PADCEV in combination with intravenous pembrolizumab for the treatment of MIBC.
- 7% (34/485) of patients who received PADCEV in combination with intravenous pembrolizumab for the treatment of locally advanced or mUC.

Because of the low occurrence of ADA, the effect of the ADA on the pharmacokinetics, pharmacodynamics, safety, and/or effectiveness of PADCEV is unknown.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with enfortumab vedotin-ejfv or the small molecule cytotoxic agent (MMAE) have not been conducted.

MMAE was genotoxic in the rat bone marrow micronucleus study through an aneugenic mechanism. This effect is consistent with the pharmacological effect of MMAE as a microtubule-disrupting agent. MMAE was not mutagenic in the bacterial reverse mutation assay (Ames test) or the L5178Y mouse lymphoma forward mutation assay.

Fertility studies with enfortumab vedotin-ejfv or MMAE have not been conducted. However, results of repeat-dose toxicity studies indicate the potential for enfortumab vedotin-ejfv to impair female and male reproductive function and fertility.

In repeat-dose toxicology studies conducted in rats for up to 13 weeks, doses ≥2 mg/kg enfortumab vedotin-ejfv (at exposures similar to the exposures at the recommended human dose) resulted in decreases in testes and epididymis weights, seminiferous tubule degeneration, spermatid/spermatocyte depletion in the testes and cell debris, sperm granuloma, and hypospermia/abnormal spermatids in the epididymis. Findings in the testes and epididymis did not reverse by the end of the recovery period.

MMAE-containing ADCs have been associated with adverse ovarian effects when administered to sexually immature animals. Adverse effects included decrease in, or absence of, secondary and tertiary ovarian follicles after weekly administration to cynomolgus monkeys in studies of 4-week duration. These effects showed a trend towards recovery 6 weeks after the end of dosing; no changes were observed in primordial follicles.

14 CLINICAL STUDIES

14.1 Urothelial Cancer

Neoadjuvant and Adjuvant Treatment of Cisplatin-Ineligible Patients with MIBC

EV-303

The efficacy of PADCEV in combination with intravenous pembrolizumab as neoadjuvant treatment and then continued after RC as adjuvant treatment was evaluated in EV-303 (NCT03924895), an open-label, randomized, multicenter trial that enrolled patients with previously untreated MIBC with predominant urothelial carcinoma histology and who were candidates for radical cystectomy (RC) with pelvic lymph node dissection (PLND) but were ineligible for or refused cisplatin-based chemotherapy. The study excluded patients with primary non-bladder (i.e., ureter, urethral, or renal pelvis) cancer of the urothelium and those with active autoimmune disease that required systemic therapy within 2 years of treatment or a medical condition that required immunosuppression.

Randomization was stratified by tumor stage (T2N0 vs T3/T4aN0 vs T1-T4aN1), cisplatin-eligibility (cisplatin-ineligible vs cisplatin-eligible but declined), and geographic region (United States vs European Union vs Rest of World).

Patients were randomized 1:1 to receive:

- Neoadjuvant PADCEV 1.25 mg/kg as an intravenous infusion on Days 1 and 8 in combination with intravenous pembrolizumab 200 mg as an intravenous infusion on Day 1 of a 21-day cycle for 3 cycles prior to surgery, followed by adjuvant PADCEV for up to 6 cycles and intravenous pembrolizumab for up to 14 cycles (21 days per cycle) (n=170).
- Immediate RC and PLND alone (n=174).

Treatment continued until completion of the treatment, disease progression, not undergoing or refusal of RC and PLND, disease recurrence in the adjuvant phase, or unacceptable toxicity. Assessment of tumor status, including CT/MRI, was performed at baseline, within 5 weeks prior to RC and PLND, and at 6 weeks post-surgery. Following RC and PLND, assessment of tumor status, including cystoscopy and urine cytology for patients who did not undergo surgery, was performed every 12 weeks up to 2 years, and every 24 weeks thereafter.

The median age was 73 years (range: 46 to 87 years); 78% were male; 78% were White, 16% were Asian, 3.2% were multiple, 1.2% were Black or African American, 0.3% American Indian or Alaska Native, and race in 1.2% was missing; 91% were not Hispanic or Latino, 6% were Hispanic or Latino, and 2.9% were not reported. Patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (57%), 1 (29%), or 2 (14%). Eighteen percent were T2N0, 77% T3/T4aN0, and 4.9% T1-T4aN1. Among the 281 patients who were ineligible for cisplatin, 72% had baseline creatinine clearance of 30-59 mL/min, 17% had ECOG PS of 2, 21% had Grade 2 or greater hearing loss, 3.9% had NYHA Class III heart failure, and 13% met more than one cisplatin-ineligibility criterion. Ninety-one percent of patients had pure urothelial carcinoma histology; 4.4% had urothelial carcinoma with squamous differentiation, 2.6% had urothelial carcinoma with glandular differentiation, and 2% had urothelial carcinoma with other variant histology.

In the overall population, 149 (88%) patients in the PADCEV in combination with intravenous pembrolizumab arm and 156 (90%) patients in the RC and PLND alone arm underwent RC and PLND.

The trial was not designed to isolate the effect of PADCEV in combination with intravenous pembrolizumab in each phase (neoadjuvant or adjuvant) of treatment.

The major efficacy outcome measure was event-free survival (EFS) as assessed by blinded independent central review (BICR). Overall survival (OS) and pathological complete response (pCR) rate as assessed by blinded independent pathology review were additional efficacy outcome measures.

The trial demonstrated statistically significant improvements in EFS and OS in patients treated with neoadjuvant and adjuvant PADCEV in combination with intravenous pembrolizumab compared with RC and PLND alone.

Table 18 and Figures 2-3 summarize the efficacy results for EV-303.

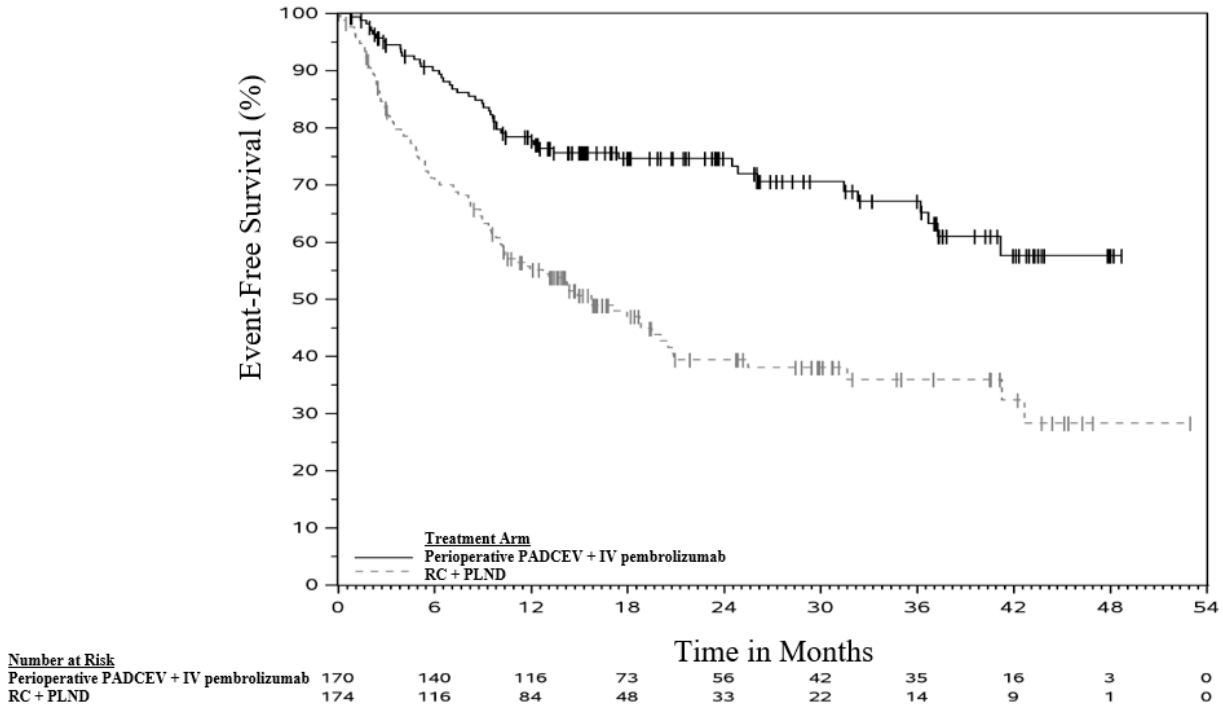
Table 18. Efficacy Results in EV-303

Endpoint	**PADCEV with intravenous pembrolizumab before and after RC with PLND n=170**	**RC with PLND alone n=174**
Event-Free Survival[1]		
Number (%) of patients with events	48 (28)	95 (55)
Median in months[2] (95% CI)	NR (37.3, NR)	15.7 (10.3, 20.5)
Hazard ratio[3] (95% CI)	0.40 (0.28, 0.57)	
p-value[4]	<0.0001	
Overall Survival		
Number (%) of patients with events	38 (22)	68 (39)
Median in months[2] (95% CI)	NR (NR, NR)	41.7 (31.8, NR)
Hazard ratio[3] (95% CI)	0.50 (0.33, 0.74)	
p-value[4]	0.0002	

NR = Not Reached.

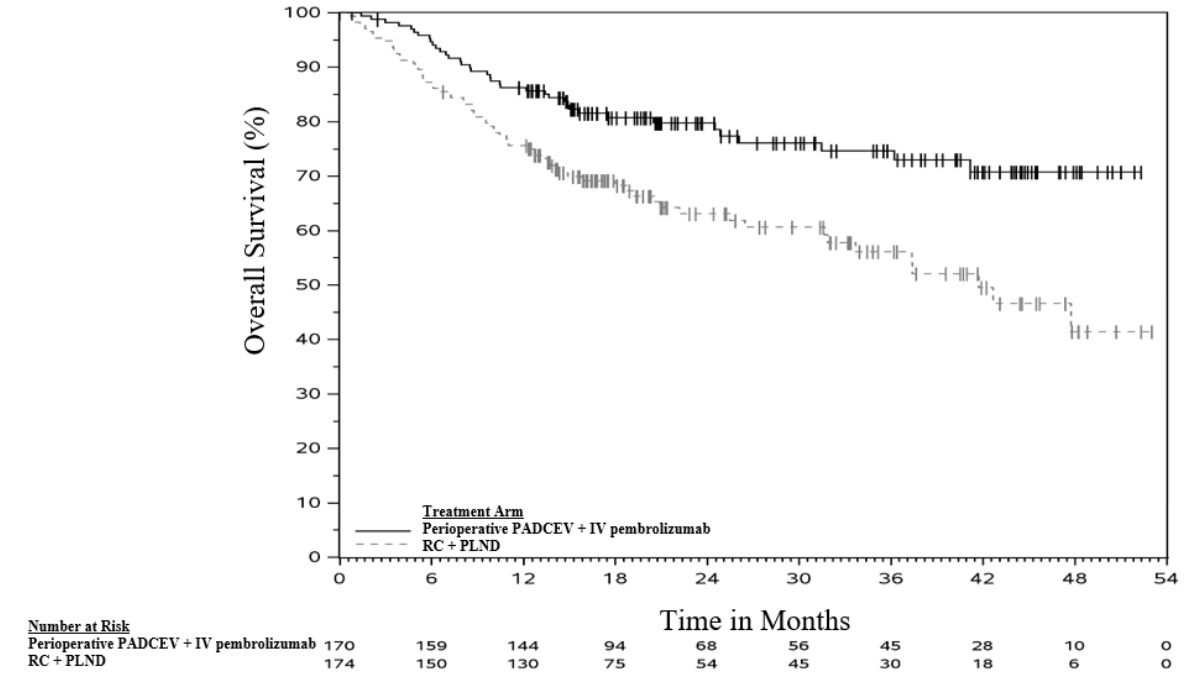
1. EFS is defined as time from randomization to the first of: disease progression preventing curative surgery, failure to undergo surgery for participants with muscle invasive residual disease, incomplete surgical resection, local or distant recurrence after surgery, or death.
2. Based on Kaplan-Meier estimates.
3. Based on stratified Cox regression model.
4. Based on stratified log-rank test.

Figure 2. Kaplan-Meier Plot of Event-Free Survival, EV-303



Number at Risk										
Perioperative PADCEV + IV pembrolizumab	170	140	116	73	56	42	35	16	3	0
RC + PLND	174	116	84	48	33	22	14	9	1	0

Figure 3. Kaplan-Meier Plot of Overall Survival, EV-303



Number at Risk										
Perioperative PADCEV + IV pembrolizumab	170	159	144	94	68	56	45	28	10	0
RC + PLND	174	150	130	75	54	45	30	18	6	0

The trial demonstrated a statistically significant difference in pCR rate (57.1% [95% CI: 49.3, 64.6] vs. 8.6% [95% CI: 4.9, 13.8]; $p<0.0001$).

Previously Untreated Locally Advanced or mUC

EV-302

The efficacy of PADCEV in combination with intravenous pembrolizumab was evaluated in EV-302 (NCT04223856), an open label, randomized, multicenter trial that enrolled 886 patients with locally advanced or mUC who received no prior systemic therapy for locally advanced or metastatic disease. Patients with active CNS metastases, ongoing sensory or motor neuropathy Grade ≥2, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms were excluded.

Patients were randomized 1:1 to receive either:

- PADCEV 1.25 mg/kg on Days 1 and 8 of a 21-day cycle followed by intravenous pembrolizumab 200 mg on Day 1 of a 21-day cycle. Treatment was continued until disease progression or unacceptable toxicity. In the absence of disease progression or unacceptable toxicity, pembrolizumab was continued for up to 2 years.
- Gemcitabine 1000 mg/m^2 on Days 1 and 8 of a 21-day cycle with cisplatin 70 mg/m^2 or carboplatin (AUC = 4.5 or 5) on Day 1 of a 21-day cycle. Treatment was continued until disease progression or unacceptable toxicity for up to 6 cycles.

Randomization was stratified by cisplatin eligibility, PD-L1 expression, and presence of liver metastases.

The median age was 69 years (range: 22 to 91 years); 77% were male; 67% were White, 22% were Asian, 1% were Black or African American, and 10% were unknown or other; 12% were Hispanic or Latino. Patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (49%), 1 (47%), or 2 (3%). Forty-seven percent of patients had a documented baseline HbA1c of <5.7%. At baseline, 95% of patients had metastatic urothelial cancer, including 72% with visceral and 22% with liver metastases, and 5% had locally advanced urothelial cancer. Eighty-five percent of patients had urothelial carcinoma (UC) histology including 6% with UC mixed squamous differentiation and 2% with UC mixed other histologic variants. Forty-six percent of patients were considered cisplatin-ineligible and 54% were considered cisplatin-eligible at time of randomization.

The major efficacy outcome measures were overall survival (OS) and progression-free survival (PFS) as assessed by blinded independent central review (BICR) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Additional efficacy outcome measures included objective response rate (ORR) as assessed by BICR.

The trial demonstrated statistically significant improvements in OS, PFS, and ORR for patients randomized to PADCEV in combination with intravenous pembrolizumab as compared to platinum-based chemotherapy. Efficacy results were consistent across all stratified patient subgroups. Table 19 and Figures 4-5 summarize the efficacy results for EV-302.

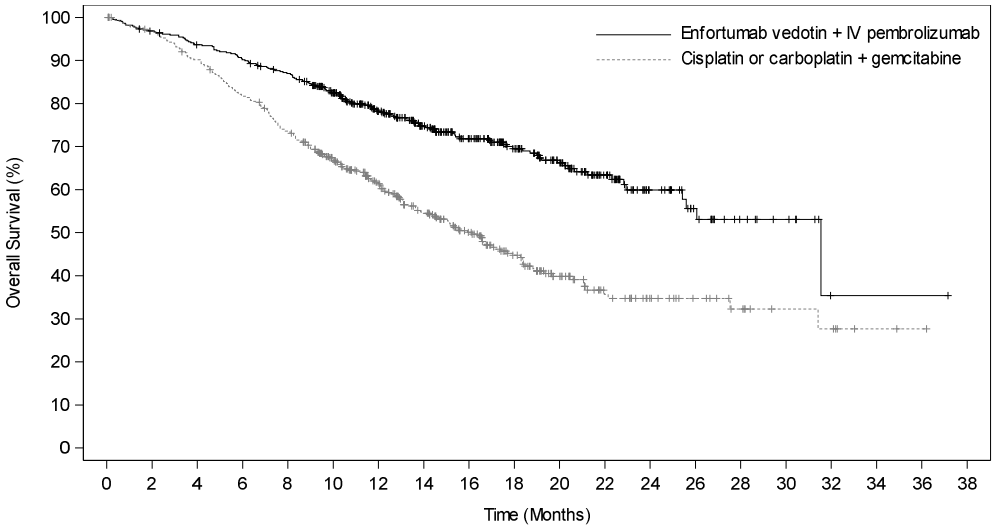
Table 19. Efficacy Results in EV-302

Endpoint	PADCEV with intravenous pembrolizumab n=442	Cisplatin or carboplatin with gemcitabine n=444
Overall Survival		
Number (%) of patients with events	133 (30.1)	226 (50.9)
Median in months (95% CI)	31.5 (25.4, NE)	16.1 (13.9, 18.3)
Hazard ratio (95% CI)[1]	0.47 (0.38, 0.58)	
p-value[2, 3]	<0.0001	
Progression-Free Survival		
Number (%) of patients with events	223 (50.5)	307 (69.1)
Median in months (95% CI)	12.5 (10.4, 16.6)	6.3 (6.2, 6.5)
Hazard ratio (95% CI)[1]	0.45 (0.38, 0.54)	
p-value[2, 3]	<0.0001	
Confirmed Objective Response Rate[4]		
ORR (%) (95% CI)	67.7 (63.1, 72.1)	44.4 (39.7, 49.2)
p-value[3, 5]	<0.0001	
Complete response rate (%)	29.1	12.5
Partial response rate (%)	38.7	32.0

NE = Not estimable.

1. Based on a stratified Cox proportional hazards model.
2. Based on stratified log-rank test.
3. Two-sided p-value.
4. Includes only patients with measurable disease at baseline (n=437 for PADCEV in combination with intravenous pembrolizumab, n=441 for chemotherapy).
5. Cochran-Mantel-Haenszel test (CMH) controlling for stratification factors.

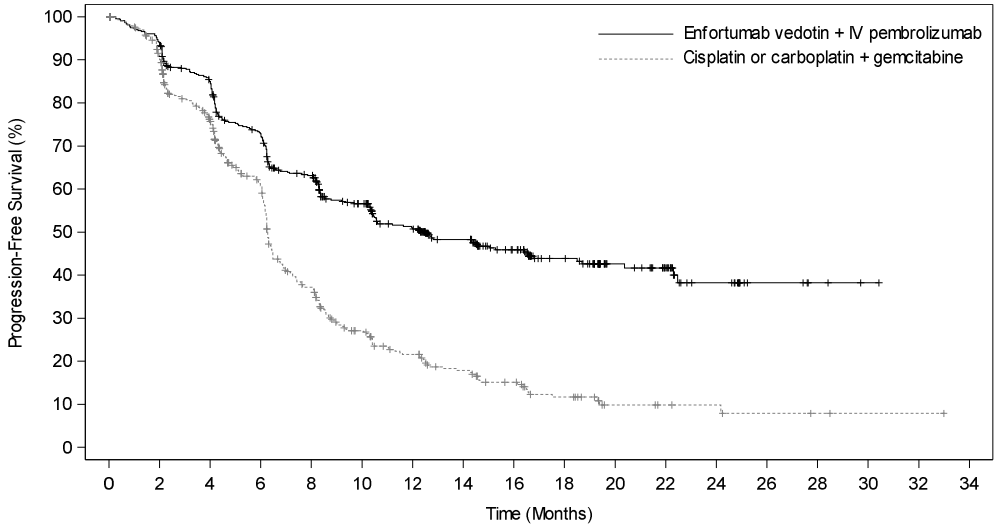
Figure 4. Kaplan-Meier Plot of Overall Survival, EV-302



N at Risk

Enfortumab vedotin + IV pembrolizumab	442	426	409	394	376	331	270	222	182	141	108	67	36	22	12	8	1	1	1
Cisplatin or carboplatin + gemcitabine	444	423	393	356	317	263	209	164	125	90	60	37	25	18	12	7	6	2	1

Figure 5. Kaplan-Meier Plot of Progression-Free Survival, EV-302



N at Risk

Enfortumab vedotin + IV pembrolizumab	442	409	361	303	253	204	167	132	102	73	45	33	17	6	3	1	
Cisplatin or carboplatin + gemcitabine	444	380	297	213	124	78	56	41	30	19	8	6	5	3	2	1	1

Cisplatin-Ineligible Patients with Previously Untreated Locally Advanced or mUC

EV-103

The efficacy of PADCEV in combination with intravenous pembrolizumab was evaluated in EV-103 (NCT03288545), an open-label, multi-cohort (dose escalation cohort, Cohort A, Cohort K) trial in patients with locally advanced or metastatic urothelial cancer who were ineligible for cisplatin-containing chemotherapy and received no prior systemic therapy for locally advanced or metastatic disease. Patients with active CNS metastases, ongoing sensory or motor neuropathy Grade ≥2, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms were excluded from participating in the trial.

Patients in the dose escalation cohort (n=5), Cohort A (n=40), and Cohort K (n=76) received PADCEV 1.25 mg/kg as an IV infusion on Days 1 and 8 of a 21-day cycle followed by intravenous pembrolizumab 200 mg on Day 1 of a 21-day cycle. Patients were treated until disease progression or unacceptable toxicity.

A total of 121 patients received PADCEV in combination with intravenous pembrolizumab. The median age was 71 years (range: 51 to 91 years); 74% were male; 85% were White, 5% were Black, 4% were Asian, and 6% were other, unknown, or not reported. Ten percent of patients were Hispanic or Latino. Forty-five percent of patients had an ECOG performance status of 1 and 15% had an ECOG performance status of 2. Forty-seven percent of patients had a documented baseline HbA1c of <5.7%. Reasons for cisplatin ineligibility included: 60% with baseline creatinine clearance of 30-59 mL/min, 10% with ECOG PS of 2, 13% with Grade 2 or greater hearing loss, and 16% with more than one cisplatin-ineligibility criteria.

At baseline, 97.5% of patients had metastatic urothelial cancer and 2.5% of patients had locally advanced urothelial cancer. Thirty-seven percent of patients had upper tract disease. Eighty-four percent of patients had visceral metastasis at baseline including 22% with liver metastases. Thirty-nine percent of patients had transitional cell carcinoma (TCC) histology; 13% had TCC with squamous differentiation and 48% had TCC with other histologic variants.

The major efficacy outcome measures were ORR and DoR as assessed by BICR according to RECIST v1.1.

The median follow-up time for the dose escalation cohort + Cohort A was 44.7 months (range: 0.7 to 52.4 months) and for Cohort K was 14.8 months (range: 0.6 to 26.2 months).

Efficacy results are presented in Table 20 below.

Table 20. Efficacy Results in EV-103, Combined Dose Escalation Cohort, Cohort A, and Cohort K

Endpoint	**PADCEV in combination with intravenous pembrolizumab n=121**
Confirmed ORR (95% CI)	68% (58.7, 76.0)
Complete response rate	12%
Partial response rate	55%

The median duration of response for the dose escalation cohort + Cohort A was 22.1 months (range: 1.0+ to 46.3+ months) and for Cohort K was not reached (range: 1.2 to 24.1+ months).

Previously Treated Locally Advanced or mUC

EV-301

The efficacy of PADCEV as a single agent was evaluated in EV-301 (NCT03474107), an open-label, randomized, multicenter trial that enrolled 608 patients with locally advanced or mUC who received prior treatment with a PD-1 or PD-L1 inhibitor and platinum-based chemotherapy. Patients were randomized 1:1 to receive either PADCEV 1.25 mg/kg on Days 1, 8, and 15 of a 28-day cycle or investigator's choice of chemotherapy. Randomization was stratified by ECOG PS (0 vs 1), region of world (Western Europe vs US vs Rest of World), and presence of liver metastasis.

Patients were excluded if they had active central nervous system (CNS) metastases, ongoing sensory or motor neuropathy ≥ Grade 2, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms.

The median age was 68 years (range: 30 to 88 years) and 77% were male. Racial demographics were reported as White (52%), Asian (33%), Black (0.7%), Native Hawaiian or Other Pacific Islander (0.2%), or not reported (15%). Nine percent of patients were Hispanic or Latino. All patients had a baseline ECOG performance status of 0 (40%) or 1 (60%). Thirty-four percent of patients had tumors located in the upper tract that included the renal pelvis and ureter. Eighty percent of patients had visceral metastases including 31% with liver metastases. Seventy-six percent of patients had pure TCC histology; 14% had TCC with other histologic variants; and 10% had other tumor histologies including adenocarcinoma and squamous cell carcinoma. The median number of prior therapies was 2 (range 1 to ≥3). Sixty-three percent of patients received prior cisplatin-based regimens, 26% received prior carboplatin-based regimens, and an additional 11% received both cisplatin and carboplatin-based regimens. Patients on the control arm received docetaxel (38%), paclitaxel (36%), or vinflunine (25%).

The major efficacy outcome measures were OS, PFS, and ORR assessed by investigator using RECIST v1.1. Efficacy results were consistent across all stratified patient subgroups.

Table 21 and Figures 6-7 summarize the efficacy results for EV-301.

Table 21. Efficacy Results in EV-301

Endpoint	**PADCEV n=301**	**Chemotherapy n=307**
Overall Survival[1]		
Number (%) of patients with events	134 (44.5)	167 (54.4)
Median in months (95% CI)	12.9 (10.6, 15.2)	9.0 (8.1, 10.7)
Hazard ratio (95% CI)	0.70 (0.56, 0.89)	
p-value	0.0014	
Progression-Free Survival[1]		
Number (%) of patients with events	201 (66.8)	231 (75.2)
Median in months (95% CI)	5.6 (5.3, 5.8)	3.7 (3.5, 3.9)
Hazard ratio (95% CI)	0.62 (0.51, 0.75)	
p-value	<0.0001	
Overall Response Rate (CR + PR)[2]		
ORR (%) (95% CI)	40.6 (34.9, 46.5)	17.9 (13.7, 22.8)
p-value	<0.0001	
Complete response rate (%)	4.9	2.7
Partial response rate (%)	35.8	15.2

1. Based on log-rank test. Stratification factors were ECOG PS, region and liver metastasis.
2. Based on Cochran-Mantel-Haenszel test. Stratification factors were ECOG PS, region and liver metastasis.

Figure 6. Kaplan-Meier Plot of Overall Survival, EV-301

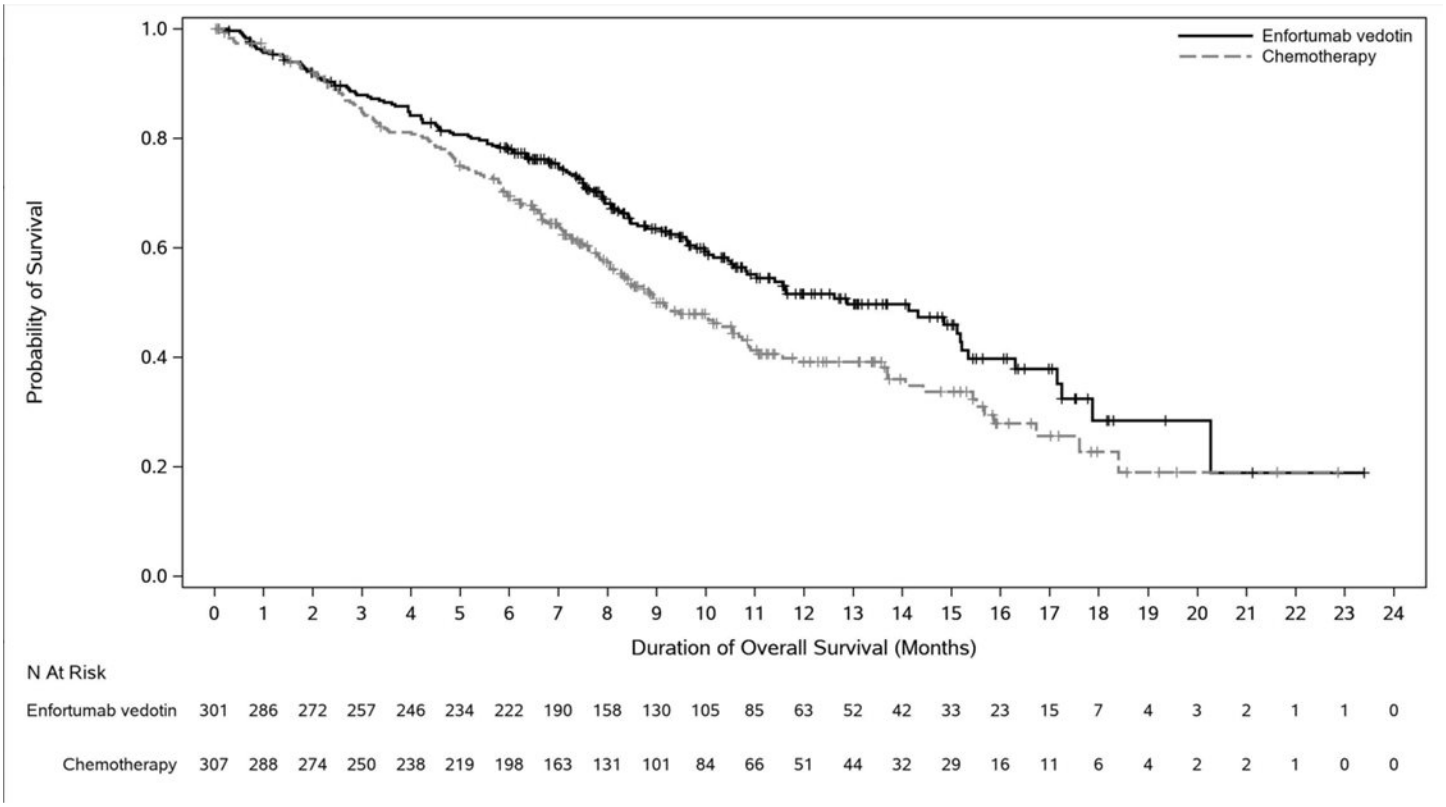
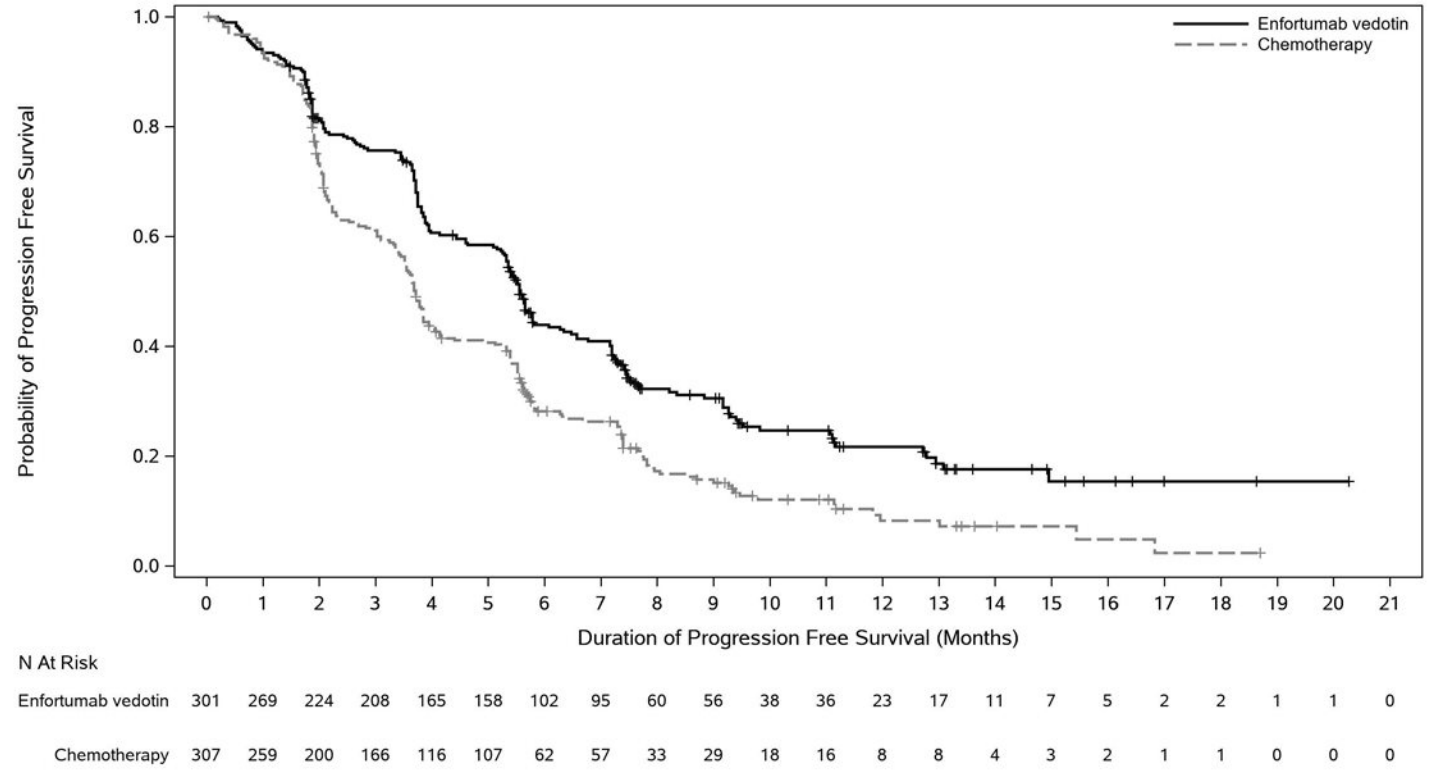


Figure 7. Kaplan-Meier Plot of Progression-Free Survival, EV-301



EV-201, Cohort 1

The efficacy of PADCEV as a single agent was also investigated in Cohort 1 of EV-201 (NCT03219333), a single-arm, multi-cohort, multicenter trial that enrolled 125 patients with locally advanced or mUC who received prior treatment with a PD-1 or PD-L1 inhibitor and a platinum-based chemotherapy. Patients were excluded if they had active central nervous system (CNS) metastases, ongoing sensory or motor neuropathy ≥ Grade 2, heart failure, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms.

PADCEV was administered at a dose of 1.25 mg/kg, as an intravenous (IV) infusion on Days 1, 8, and 15 of each 28-day cycle.

The median age was 69 years (range: 40 to 84 years) and 70% were male. Racial demographics were reported as White (85%), Asian (9%), Black (2%), Other (0.8%), or not reported (4%). Four percent of patients were Hispanic or Latino. All patients had a baseline Eastern Cooperative Oncology Group (ECOG) performance status of 0 (32%) or 1 (68%). Ninety percent of patients had visceral metastases including 40% with liver metastases. Approximately two-thirds (67%) of patients had pure transitional cell carcinoma (TCC) histology; 33% had TCC with other histologic variants. The median number of prior systemic therapies was 3 (range: 1 to 6). Sixty-six percent of patients received prior cisplatin-based regimens, 26% received prior carboplatin-based regimens, and an additional 8% received both cisplatin and carboplatin-based regimens.

The major efficacy outcome measures were confirmed objective response rate (ORR) and duration of response (DOR) assessed by BICR using RECIST v1.1.

Efficacy results are presented in Table 22.

Table 22. Efficacy Results in EV-201, Cohort 1 (BICR Assessment)

Endpoint	**PADCEV n=125**
Confirmed ORR (95% CI)	44% (35.1, 53.2)
Complete Response Rate (CR)	12%
Partial Response Rate (PR)	32%
Median[1] Duration of Response, months (95% CI)	7.6 (6.3, NE)

NE = not estimable.

1. Based on patients (n=55) with a response by BICR.

Previously Treated Cisplatin-Ineligible Patients with Locally Advanced or mUC

EV-201, Cohort 2

The efficacy of PADCEV as a single agent was also evaluated in Cohort 2 of EV-201, a single-arm, multi-cohort, multicenter trial in 89 patients with locally advanced or mUC who received prior treatment with a PD-1 or PD-L1 inhibitor and were cisplatin-ineligible and did not receive platinum in the locally advanced or metastatic setting. Patients were excluded if they had active CNS metastases, ongoing sensory or motor neuropathy ≥ Grade 2, heart failure, or uncontrolled diabetes defined as hemoglobin A1C (HbA1c) ≥8% or HbA1c ≥7% with associated diabetes symptoms.

PADCEV was administered at a dose of 1.25 mg/kg, as an intravenous (IV) infusion on Days 1, 8, and 15 of each 28-day cycle.

The median age was 75 years (range: 49 to 90 years), 74% were male. Racial demographics were reported as White (70%), Asian (22%), or not reported (8%). One percent of patients were Hispanic or Latino. Patients had a baseline ECOG performance status of 0 (42%), 1 (46%), and 2 (12%). Forty-three percent of patients had tumors located in the upper tract that included the renal pelvis and ureter. Seventy-nine percent of patients had visceral metastases and 24% had liver metastases.

Reasons for cisplatin ineligibility included: 66% with baseline creatinine clearance of 30-59 mL/min, 7% with ECOG PS of 2, 15% with Grade 2 or greater hearing loss, and 12% with more than one cisplatin-ineligibility criteria. Seventy percent of patients had TCC histology; 13% had TCC with squamous differentiation and 17% had TCC with other histologic variants.

The median number of prior systemic therapies was 1 (range: 1 to 4).

Efficacy results are presented in Table 23 below.

Table 23. Efficacy Results in EV-201, Cohort 2 (BICR Assessment)

Endpoint	**PADCEV n=89**
Confirmed ORR (95% CI)	51% (39.8, 61.3)
Complete Response Rate (CR)	22%
Partial Response Rate (PR)	28%
Median[1] Duration of Response, months (95% CI)	13.8 (6.4, NE)

NE = not estimable.

1. Based on patients (n=45) with a response by BICR.

15 REFERENCES

1. "OSHA Hazardous Drugs." OSHA. http://www.osha.gov/SLTC/hazardousdrugs/index.html

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

PADCEV (enfortumab vedotin-ejfv) 20 mg and 30 mg are supplied as a sterile, preservative-free, white to off-white lyophilized powder in single-dose vials. PADCEV vials are available in the following packages:

- Carton of one 20 mg single-dose vial (NDC 51144-020-01)
- Carton of one 30 mg single-dose vial (NDC 51144-030-01)

Storage

Store PADCEV vials refrigerated at 2ºC to 8ºC (36ºF to 46ºF) in the original carton. Do not freeze. Do not shake.

Special Handling

PADCEV is a hazardous drug. Follow applicable special handling and disposal procedures.[1]

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Skin Reactions

Inform patients that severe skin reactions including SJS and TEN with fatal outcomes have occurred after administration of PADCEV, predominantly during the first cycle of treatment but may occur later.

Advise patients to contact their healthcare provider immediately if they develop new target lesions, progressively worsening skin reactions, severe blistering, or peeling of the skin *[see Boxed Warning and Warnings and Precautions (5.1)]*.

Hyperglycemia

Inform patients about the risk of hyperglycemia and how to recognize associated symptoms *[see Warnings and Precautions (5.2)]*.

Pneumonitis/ILD

Advise patients to immediately report new or worsening respiratory symptoms *[see Warnings and Precautions (5.3)]*.

Peripheral Neuropathy

Inform patients to report to their healthcare provider any numbness and tingling of the hands or feet or muscle weakness *[see Warnings and Precautions (5.4)]*.

Ocular disorders

Advise patients to contact their healthcare provider if they experience any visual changes *[see Warnings and Precautions (5.5)]*. In order to prevent or treat dry eyes, advise patients to use artificial tear substitutes.

Infusion Site Extravasation

Inform patients that infusion site reactions have occurred after administration of PADCEV. These reactions generally occurred immediately after administration but, in some instances, had a delayed onset (e.g., 24 hours). Instruct patients to contact their healthcare provider immediately if they experience an infusion site reaction *[see Warnings and Precautions (5.6)]*.

Embryo-Fetal Toxicity

Advise pregnant women and females of reproductive potential of the potential risk to the fetus. Advise females to inform their healthcare providers of a known or suspected pregnancy *[see Warnings and Precautions (5.7) and Use in Specific Populations (8.1)]*.

Females and Males of Reproductive Potential

Advise female patients of reproductive potential to use effective contraception during treatment with PADCEV and for 2 months after the last dose. Advise male patients with female partners of reproductive potential to use effective contraception during treatment with PADCEV and for 4 months after the last dose *[see Use in Specific Populations (8.3)]*.

Lactation

Advise women not to breastfeed during treatment with PADCEV and for 3 weeks after the last dose *[see Use in Specific Populations (8.2)]*.

Infertility

Advise females and males of reproductive potential that PADCEV may impair fertility *[see Use in Specific Populations (8.3)]*.

Manufactured and Marketed by:
Astellas Pharma US, Inc.
Northbrook, Illinois 60062

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Seagen Inc.
Bothell, WA 98021
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PATIENT INFORMATION
PADCEV® (PAD-sev)
(enfortumab vedotin-ejfv)
for injection

If your healthcare provider prescribes PADCEV in combination with the medicines pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph, also read the Medication Guide that comes with these medicines for additional important information.

What is the most important information I should know about PADCEV?
PADCEV may cause serious side effects, including:
Skin reactions. Skin reactions including severe skin reactions have happened in people treated with PADCEV and may be more common when PADCEV is given with pembrolizumab. In some cases, these severe skin reactions have caused death. Most severe skin reactions occurred during the first cycle of treatment but may happen later. Your healthcare provider will monitor you, may stop your treatment with PADCEV completely or for a period of time (temporarily), may change your dose, and may prescribe medicines if you get skin reactions. Tell your healthcare provider right away if you develop any of these signs of a new or worsening skin reaction:

- target lesions (skin reactions that look like rings)
- rash or itching that continues to get worse
- blistering or peeling of the skin
- painful sores or ulcers in mouth or nose, throat, or genital area
- fever or flu-like symptoms
- swollen lymph nodes

See **"What are the possible side effects of PADCEV?"** for more information about side effects.

What is PADCEV?
PADCEV is a prescription medicine used to treat adults with bladder cancer and cancers of the urinary tract (renal pelvis, ureter, or urethra).

- PADCEV may be used with pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph before and after the surgical removal of your bladder when:
  - your bladder cancer has spread into the muscle layer of the bladder (muscle invasive bladder cancer [MIBC]) but not to other parts of the body, **and**
  - you are not able to receive chemotherapy that contains the medicine cisplatin.
- PADCEV may be used with pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph when your bladder or urinary tract cancer has spread or cannot be removed by surgery (locally advanced or metastatic).
- PADCEV may be used alone when your bladder or urinary tract cancer has spread or cannot be removed by surgery (locally advanced or metastatic) if you:
  - have received PD-1 or PD-L1 immunotherapy medicine **and** chemotherapy that contains platinum, **or**
  - are not able to receive a chemotherapy that contains cisplatin **and** you have received 1 or more prior therapies.

It is not known if PADCEV is safe and effective in children.

Before receiving PADCEV, tell your healthcare provider about all of your medical conditions, including if you:

- are currently experiencing numbness or tingling in your hands or feet
- have a history of high blood sugar or diabetes
- have liver problems
- are pregnant or plan to become pregnant. PADCEV can harm your unborn baby. Tell your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with PADCEV.
  Females who are able to become pregnant:
  - Your healthcare provider should do a pregnancy test before you start treatment with PADCEV.
  - You should use an effective method of birth control during your treatment and for at least 2 months after the last dose of PADCEV.

  Males with a female sexual partner who is able to become pregnant:
  - If your female partner is pregnant, PADCEV can harm the unborn baby.
  - You should use an effective method of birth control during your treatment and for at least 4 months after the last dose of PADCEV.
- are breastfeeding or plan to breastfeed. It is not known if PADCEV passes into your breast milk. Do not breastfeed during treatment and for 3 weeks after the last dose of PADCEV.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Taking PADCEV with certain other medicines may cause side effects.

How will I receive PADCEV?

- PADCEV will be given to you by intravenous (IV) infusion into your vein over 30 minutes.
- PADCEV is given over periods of time called “cycles”.
- If you receive PADCEV with pembrolizumab or pembrolizumab and berahyaluronidase alfa-pmph:
  - Each cycle is 21 days.
  - You will receive PADCEV on days 1 and 8 of every cycle.
- If you receive PADCEV alone:
  - Each PADCEV cycle is 28 days.
  - You will receive PADCEV on days 1, 8, and 15 of every cycle.
- Your healthcare provider will decide how many treatment cycles you need.
- Your healthcare provider may do blood tests regularly during treatment with PADCEV.

What are the possible side effects of PADCEV?

PADCEV may cause serious side effects, including:

- **See “What is the most important information I should know about PADCEV?”**
- **High blood sugar (hyperglycemia).** An increase in blood sugar is common during treatment with PADCEV. Severe high blood sugar, a serious condition called diabetic ketoacidosis (DKA), and death have happened in people with and without diabetes, treated with PADCEV. Tell your healthcare provider right away if you get any symptoms of high blood sugar, including:
  - frequent urination
  - increased thirst
  - blurred vision
  - confusion
  - it becomes harder to control your blood sugar
  - drowsiness
  - loss of appetite
  - fruity smell on your breath
  - nausea, vomiting, or stomach pain
- **Lung problems.** PADCEV may cause severe or life-threatening inflammation of the lungs that can lead to death. These severe problems may happen more often when PADCEV is given in combination with pembrolizumab. Tell your healthcare provider right away if you get new or worsening symptoms, including trouble breathing, shortness of breath, or cough.
- **Nerve problems.** Nerve problems called peripheral neuropathy are common during treatment with PADCEV and can also sometimes be severe. Nerve problems may happen more often when PADCEV is given in combination with pembrolizumab. Tell your healthcare provider right away if you get new or worsening numbness or tingling in your hands or feet or muscle weakness.
- **Eye problems.** Certain eye problems are common during treatment with PADCEV. Tell your healthcare provider right away if you get dry eyes, increased tearing, blurred vision, or any vision changes. You may use artificial tear substitutes to help prevent or treat dry eyes.
- **Leakage of PADCEV out of your vein into the tissues around your infusion site (extravasation).** If PADCEV leaks from the injection site or the vein into the nearby skin and tissues, it could cause an infusion site reaction. These reactions can happen right after you receive an infusion, but sometimes may happen days after your infusion. Tell your healthcare provider or get medical help right away if you notice any redness, swelling, itching, blister, peeling skin, or discomfort at the infusion site.

Your healthcare provider may decrease your dose of PADCEV, or temporarily or completely stop your treatment with PADCEV if you get severe side effects.

The most common side effects of PADCEV when used in combination with pembrolizumab include:

- changes in liver function and kidney function tests
- rash. **See “What is the most important information I should know about PADCEV?”**
- increased sugar (glucose) in the blood. **See “High blood sugar (hyperglycemia)” above.**
- numbness or tingling in your hands or feet. **See “Nerve problems” above.**
- increased lipase (a test done to check your pancreas)
- decreased white blood cell, red blood cell, and platelet counts
- tiredness
- decreased sodium, phosphate, and protein (albumin) in the blood
- itching
- diarrhea
- hair loss
- decreased weight
- decreased appetite
- increased uric acid in the blood
- increased or decreased potassium
- dry eye. **See “Eye problems” above.**
- nausea
- constipation
- change in sense of taste
- urinary tract infection

The most common side effects of PADCEV when used alone include:

- increased sugar (glucose) in the blood. **See "High blood sugar (hyperglycemia)" above.**
- changes in liver and kidney function tests
- decreased white blood cell, red blood cell, and platelet counts
- rash. **See "What is the most important information I should know about PADCEV?"**
- tiredness
- numbness or tingling in your hands or feet. **See "Nerve problems" above.**
- decreased protein (albumin), sodium, and phosphate in the blood
- hair loss
- decreased appetite
- diarrhea
- nausea
- itching
- increased uric acid in the blood
- dry eye. **See "Eye problems" above.**
- change in sense of taste
- constipation
- increased lipase (a blood test done to check your pancreas)
- decreased weight
- stomach (abdominal) pain
- dry skin

PADCEV may cause fertility problems in females and males, which may affect the ability to have children. Talk to your healthcare provider if you have concerns about fertility.
These are not all of the possible side effects of PADCEV.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

General information about the safe and effective use of PADCEV.
Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. You can ask your pharmacist or healthcare provider for information about PADCEV that is written for healthcare professionals.

What are the ingredients in PADCEV?
Active ingredient: enfortumab vedotin-ejfv
Inactive ingredients: histidine, histidine hydrochloride monohydrate, polysorbate 20, and trehalose dihydrate.

Manufactured and Marketed by: Astellas Pharma US, Inc., Northbrook, Illinois 60062
Distributed and Marketed by: Seagen Inc., Bothell, WA 98021
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For more information, go to www.padcev.com or call 1-888-472-3238
08368-EV-US

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 11/2025